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Perspective Article

Hylonome

Animal models relevant to cementless joint replacement

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Abstract

This review focuses on animal models used to study certain aspects of "cementless" joint replacement. Implants used in this application are designed to become attached to the host skeleton through either bone ingrowth into porous surfaces or bone apposition (ongrowth) onto other types of surfaces. Biological fixation of cementless joint replacement implants relies on intramembranous bone regeneration. We describe a framework for understanding research design in light of the type of research questions now being asked. In particular, species choice, implant design and placement, and experimental endpoints are described in some detail. We provide a summary of recent studies specifically focused on implant fixation, demonstrating that most work is still at the morphological and biomechanical levels with little understanding at the molecular level. We also provide a more comprehensive listing of studies using hip and knee replacement models, demonstrating that most work is focused on the interface, and responses of the immediately adjacent trabecular bone and the more distant cortical bone. We conclude by encouraging investigators to design their experiments so that there is enough power to answer a limited number of questions as opposed to providing limited data on a broader number of issues.

Keywords: Animal Models, Total Hip Replacement, Total Knee Replacement, Bone Regeneration, Implants

Introduction

Joint replacement is now considered one of the most successful surgical procedures because of reliable pain relief and return to function[1]. Currently, in the U.S. alone a conservative estimate is that more than 400,000 total hip and knee replacements are performed annually. In addition, a significant number of shoulder and small joint replacements provide pain relief and improved function in the upper extremity and foot. A smaller number of ankle replacements are performed each year. The basis of this success is a considerable research effort, including a large body of work relying on animal models[2].

Here, we focus on certain aspects of "cementless" joint replacement. These implants are designed to become attached to the host skeleton through either bone ingrowth into porous surfaces or bone apposition (ongrowth) onto other types of surfaces. Sometimes, these processes are called biological fixation or osseointegration. The term osseointegration has been borrowed from dentistry[3], where initially the term referred specifically to apposition of bone to titanium implants at the light microscopic level and implied the use of screw-shaped, commercially pure titanium devices placed with minimal trauma to the host bone in a two-stage surgical procedure. Use of the term osseointegration has now taken on a more general meaning to include fixation of implants by bone ingrowth or apposition in the absence of acrylic bone cement or a fibrous tissue interface.

The implants used today are designed to provide pain relief and improved function indefinitely, but there is increasing interest in providing biological reconstruction for injured or damaged joints[4]. This is already being accomplished with some success today through the use of osteochondral allografts and cartilage cell transplantation for relatively small lesions. However, for the extensive damage present in end-stage osteoarthritis, the most common indication for replacement of the hip or knee and certain other conditions including rheumatoid arthritis and osteonecrosis of the major weight-bearing joints, joint replacement with mechanical devices remains the most important option.

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In addition to the work on joint replacement, there has been extensive use of animal models in orthopedics to investigate the use of implants for other indications, especially fracture repair and spinal fusion[5,6]. In these two indications and others, including even joint replacement, the definition of an implant is changing from a purely mechanical device (e.g., the femoral component of a hip replacement or a fracture fixation plate) to a biological device (e.g., a bone graft substitute used in conjunction with joint replacement or spinal fusion). While the mechanical devices are meant in many cases to endure the patient's lifetime, the biological replacements are now being designed to be resorbed and replaced by functioning host tissue.

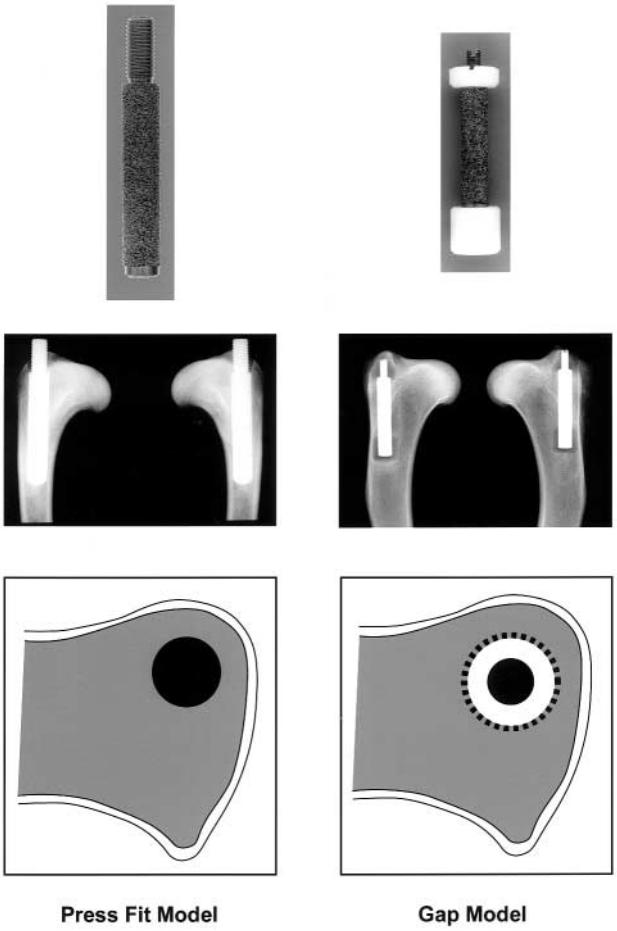

Figure 1. Two types of non-weight-bearing implants are shown. The top panels show a press-fit implant on the left and a gap implant on the right. The middle panels show these implants as placed in the proximal humerus of the dog. The lower panels are schematics showing the intimate apposition of the implant (black circle) to the host bone on the left and the presence of an initial gap on the right. (Adapted from DR Sumner, TMTurner, RH Pierson, H Kienapfel, RM Urban, EJ Liebner, and JO Galante. Effects of radiation on fixation of non-cemented porous-coated implants in a canine model. J Bone Joint Surg [Am] 72-A:1527-1533, 1990 and H. Kienapfel, DR Sumner, TM Turner, RM Urban, and JO Galante. Efficacy of autograft and freeze-dried allograft to enhance fixation of porous-coated implants in the presence of interface gaps. J Orthop Res 10:423-433, 1992).

Here, we describe animal models used to study some aspects of cementless joint replacement, specifically implant fixation and the response of the host tissue to the presence of the implant, especially the functional adaptation of the adjacent trabecular and cortical bone. We have not attempted to include thorough discussions of animal models used to address other topics relevant to joint replacement such as particulate debris[7] and prosthetic infection[8,9].

Cementless fixation

Biological fixation of cementless joint replacement implants relies on intramembranous bone regeneration, whether the tissue level mechanism is through bone ingrowth into a porous structure or bone ongrowth onto the surface of the implant[10-12]. This type of fixation occurs if the implant (i) is made from a biocompatible material, (ii) has the appropriate surface characteristics, (iii) is mechanically stable, (iv) is in close initial contact with the host bone and (v) the implantation site is not infected. In addition to these customarily recognized requirements for bone ingrowth/ongrowth in orthopedics, in dentistry the need to minimize trauma to the host bone is considered a key surgical variable[3]. Apparently, the use of porous coatings and other surface modifications in orthopedic implants has lessened the need to minimize trauma to the host skeleton at the time of surgery as well as the need to avoid immediate load-bearing. Enough information now exists from clinical studies and retrieved implants to indicate that cementless fixation with orthopedic implants does occur through bone ingrowth/ongrowth, with clinical results now often comparable to those achieved with the use of bone cement[12].

With both bone ingrowth and bone ongrowth/apposition, the long-term fixation is dependent upon a biological response from the host, specifically bone formation through the intramembranous pathway[10]. Indeed, the early work with osseointegration was based on studies of intramembranous bone regeneration[13]. The host skeleton forms woven bone as a normal response to the surgically induced damage created to prepare the anatomical site for the implant. An implant placed in this environment can then become fixed to the host if the conditions described above are present.

Research questions and research design

Research questions addressed with animal models include the appropriate implant surface characteristics (e.g., porous coating microarchitecture, surface chemistry and surface roughness), the effects of interface motion and gaps, the effects of adjuvant therapies used during joint reconstruction, and the role of bone grafts, bone graft substitutes and growth factors in enhancing implant fixation. In addition, there has been considerable interest in the functional adaptation of the host skeleton to the altered mechanical environment engendered by the presence of the implant. A number of reviews in the literature describing

many of these studies are currently available[10-12,14-20]. In this section, we provide a brief review of methodological issues, including species choice, implant design and placement, and experimental endpoints. Additional methodological issues that we describe in some detail elsewhere[19] include use of the contralateral bone as a control, sample size, and the time points to be examined.

Species choice

The most common species in use today include the dog and the rabbit. Less commonly used species include the goat, sheep, rat, mouse, pig and horse. Occasionally, primate models are used. Choice of the appropriate species is highly dependent upon the nature of the research question. For instance, if one were interested in gene expression at the interface, then a mouse or rat model would be helpful because of the availability of probes for these species. On the other hand, these species have not been used to study other issues, such as fixation in the presence of implant weight-bearing, where larger species are used.

Implant design and placement

In vivo models relevant to the function of joint replacement implants may be categorized as either non-weight-bearing or weight bearing. By definition, the non-weight-bearing devices are not directly loaded, are usually implanted for short periods of study (days to weeks) and are used to investigate implant material or the bone-implant interface isolated from the effects of cyclic weight-bearing. Most often, these models have been used to examine materials, coatings or surface modifications or the effects of treatments that may inhibit or enhance bone ingrowth. If a material or surface structure appears promising in a non-weight-bearing application, the next consideration is to test the concept under the influence of cyclic weight-bearing, usually a segmental replacement or joint replacement model (see below).

Non-weight-bearing implants can be implanted so that there is a press-fit with the host bone (i.e., initial intimate apposition between the implant surface and bone) or with an initial interfacial gap or defect (Fig. 1). The latter method is a simple means to create a model of inhibited implant fixation in which the ability of various surface treatments or materials to restore normal fixation can be tested. These implants can be placed with the long axis of the implant and bone aligned ("axial" placement) or with these two axes orthogonal ("transcortical" placement) (Fig. 2). The axial devices may be inserted into only the distal or proximal metaphyseal bone or through all regions of the bone, metaphyseal and diaphyseal. Transcortical devices can be placed in diaphyseal or metaphyseal regions, as well. Thus, the device geometry may allow apposition to only metaphyseal trabecular bone or to both metaphyseal trabecular bone and the endosteal cortical surface of the diaphysis. Our belief is that axial and transcortical metaphyseal implants provide more clinically relevant information than transcortical diaphyseal implants because most joint replacement implants are placed within a trabecular bone bed (e.g., the acetabular component in total hip replacement and the tibial and femoral components in total knee replacement) or within the medullary cavity (e.g., the femoral components in total hip replacement).

A number of authors are now using bone chamber models [21-26]. These models have certain advantages including the ability to perform vital microscopy and to make repeated tissue harvests over time. They have not been used as far as we are aware to study bulk implants, but the studies do contribute to understanding mechanisms of bone regeneration.

Recently, controlled motion models have been developed so that a major limitation of non-weight-bearing implants, lack of replication of load distribution from a weight-bearing prosthetic device to the bone, can be addressed[27-29]. These models also make it possible to test specific hypotheses about interface motion and biological fixation.

Another model system that bridges some of the differences between non-weight-bearing and joint replacement models is the use of devices that communicate with the joint[30,31]. For instance, this type of model has been used to investigate the role of particulate debris on cementless interfaces without the compounding effects of weight bearing and component movement. Controlled motion can also be imparted to this type of model[32].

Segmental replacement models, first developed in response to the need to replace large regions of long bone diaphyses severely injured by trauma are weight-bearing devices relevant to total joint replacement[33-35]. These models have been developed in the dog and other species such as primates, goats or sheep.

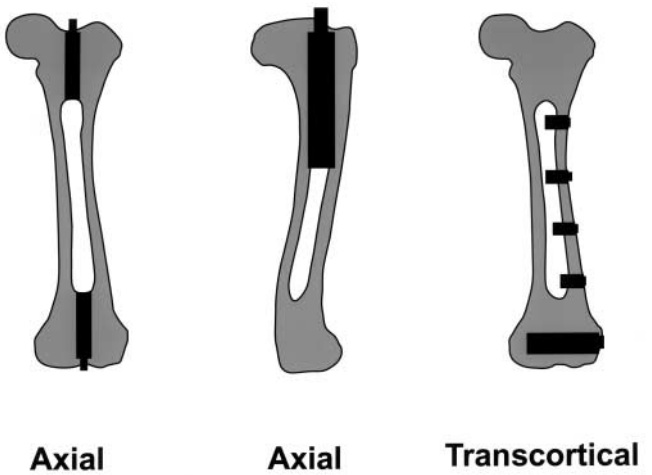

Figure 2. Schematic showing placement of axial and transcortical non-weight bearing implants for investigation of bone ingrowth. (Adapted from DR Sumner, TM Turner, and RM Urban. Animal models of bone ingrowth and joint replacement. In: Animals Models in Orthopedic Research, edited by YH An and RJ Friedman. CRC Press, Boca Raton, Fla; 1999:407-425).

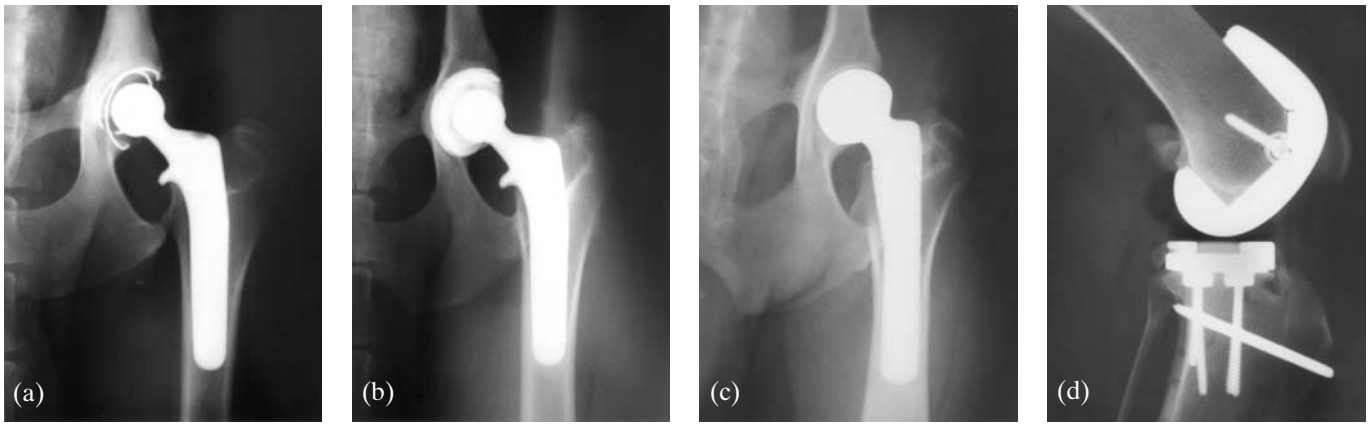

Figure 3. In vivo radiographs of three canine hip replacement models and one canine knee replacement model used by the authors. (a) a total hip replacement in which a cemented acetabular component is matched with a cementless femoral component, (b) a total hip replacement in which both the acetabular and femoral components are cementless, (c) a hemiarthroplasty in which only a femoral component is used with the head matched to the size of the intact acetabulum, and (d) a cementless knee replacement model with cementless femoral and tibial components. (From DR Sumner, TM Turner, and RM Urban. Animal models of bone ingrowth and joint replacement. In: Animals Models in Orthopedic Research, edited by YH An and RJ Friedman. CRC Press, Boca Raton, Fla; 1999:407-425).

A more common weight-bearing model, particularly in recent years, has been hip replacement (Fig. 3). This has been applied in two forms. One is a total hip replacement with both acetabular and femoral components being inserted. The other is a hip replacement hemiarthroplasty in which only the femoral head is replaced, thereby avoiding the potential complications of an acetabular component. The use of any joint replacement device in an animal model allows that device to experience the cyclic loading of ambulation both for the prosthetic device materials as well as the bone-implant interface. Although different surgical approaches have been utilized for the implantation of hip replacement components, this is a reliable model which can provide a very successful clinical function provided proper implantation of the device is achieved.

Variations on the bone-implant interface have also been studied by allowing the presence of only a press-fit or, alternatively, the development of defects in the bone adjacent to the implant. Thus, hip arthroplasties may be implanted as a press-fit device with the components being impacted into an undersized prepared cavity or as a gap model in which control defects are developed or created adjacent to the prosthetic bone interface. These defect models have been used to test various bone grafts and bone graft substitutes.

A further modification of the weight-bearing prosthetic joint model is the development of revision models that replicate the bony environment developed in the site surrounding a failed prosthetic device. The altered bony environment includes the presence of macrophage-laden granulomas rather than bone marrow at the site of implantation[36]. Use of the primary and revision hip replacement models is detailed below.

Total knee replacement models have been reported, but much less frequently than total hip replacement models (Fig. 3). Most of these studies have focused on the bone-implant interface and are described in more detail below.

Experimental endpoints

Most studies rely on morphological or mechanical endpoints. An example of a morphological endpoint is the volume fraction of bone ingrowth into a porous coating[37]. For implants lacking a porous coating, the researchers usually develop an index of bone apposition. Other morphological

Question	ENDPOINT		
	Molecular/Gene Expression	**Morphology**	**Mechanical**
surface design (porous coating type, surface roughness, surface composition)		(71-91)	(77,78,80,81,83,84,91-94)
growth factors, bone grafts, bone graft substitutes	(95-97)	(21-23,96-126)	(98,100,105,106,109,122,123)
host factors		(83,127-130)	(83)

Table 1. Selected studies involving non-weight-bearing models published since 1998.

observations include descriptions of the soft tissue at the interface[38] and bone tissue kinetics[39], and it is likely that techniques to better understand gene expression (such as in situ hybridization and immunohistochemistry) will be used in the future. In addition, morphological measurements to describe the amount and architecture of bone that forms in the vicinity of the implant[40] or of the surrounding cortical bone[41] are also used. Typical mechanical endpoints include the strength of fixation of the implant to the host bone[42] or the stability of the implant[43]. The former mechanical test is often used in non - weight - bearing models, while the latter is used in joint replacement models.

Question	ENDPOINT		
	Morphology	**Mechanical**	**Biomaterial Performance**
Interface	(31,36,41,51,54 131-193)	(134,136,149,157,164, 165,169,172,174, 183,185,194-197)	(44-47,51,52-55)
Trabecular bone	(36,41,132, 144-147,150,151,162, 166,171,174,198)	(199)	
Cortical Bone	(36,41,51,137,139,141, 142,144,146,148,150, 165,168,170-173,183, 191,198,200-207)	(165,170,172,173, 196,199,205,206, 208-210)	

Table 2. List of in vivo hip replacement models, sorted according to type of question and type of endpoint. In addition, the last part of the table lists models in which the primary endpoint was performance of the biomaterial.

Summary

The choice of model depends upon the question being asked. For instance, if one is interested in testing whether a new surface design will support bone ingrowth/apposition or fixation, the simplest approach is to use a non-weight-bearing, press-fit model. In contrast, if one is questioning whether or not a new surface design, growth factor or bone graft substitute will enhance implant fixation, then the most efficient course of action would be to use models in which fixation is inhibited, perhaps progressing from simple to complex models (e.g., a non-weight-bearing gap model to a revision total hip replacement model).

Listing of non-weight-bearing animal models used to examine fixation only

Table 1 provides a sampling of studies using in vivo models reported since 1998 that examine issues related to implant fixation. The survey is certainly not exhaustive, but is representative of the type of work now being performed. Most of the studies derive their motivation from orthopedics, but some are craniofacial in nature. The studies in this table used non-weight-bearing models. Studies involving total joint replacement models are described later in this review. We have organized the studies according to the type of question being asked and the type of endpoint used in the experiment. It is obvious from Table 1 that there is considerable interest in the design of the implant surface and the use of growth factors, bone grafts and bone graft substitutes to enhance fixation. There have been a few studies examining host factors such as the effect of estrogen depletion on implant fixation. Endpoints used by most investigators can be broadly classified as morphological. There is very little work to date on the molecular biology of implant fixation.

Listing of studies using hip replacement models

Table 2 summarizes how total hip replacement models have been used. This table provides a comprehensive summary and is not restricted to the last two years because the total number of reports using these types of models is not nearly as great as the number for the non-weight-bearing models.

With the hip replacement models, most of the attention has been on morphological and biomechanical responses with an emphasis on one or more of three primary regions: (i) the interface, (ii) the adjacent tissue (usually medullary contents or trabecular bone) or (iii) the host cortical bone. While this classification scheme works for most studies, in some the focus has been elsewhere, such as the articular cartilage after hemiarthroplasty[44-47], cement restrictors[48], and embolism[49,50]. A few studies have focused on biomaterial performance with little or no attention paid to the biological response[44-47,51-55].

Models of knee replacement

Knee models are much less common and it is not necessary to summarize the studies in tabular format. One of the early studies used a knee model to characterize the mechanical properties of fibrous tissue at the bone cement-bone interface[56]. Later studies used these models to investigate various interface phenomena, including the potential to establish bone ingrowth fixation[57-60].

More recently, knee models have been used to investigate the role of implant design on osseointegration or mechanical stability[61-64], bone grafting[65], wear of articular cartilage[66], embolism[67], hemorrhage control[68], wear debris[69], and infection[70].

Conclusion

It should be clear that there is no single model to be recommended because model choice depends upon the research question. In general, our view is that in designing an experiment it is more important to answer a limited number of questions than to have some information about many questions with no definitive answer. Practically, this usually means limiting the number of time points studied or the number of materials investigated so that adequate sample sizes can be used.

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References

1. Praemer A, Furner Sand Rice DP. Musculoskeletal conditions in the United States. American Academy of Orthopaedic Surgeon, Rosemont, Illinois; 1999.
2. An YH, Friedman RJ. Animal models in orthopaedic research. CRC Press, Boca Raton; 1999.
3. Albrektsson T, Branemark PI, Hansson HA, Lindstrom J. Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man. Acta Orthop Scand 1981; 52:155-170.
4. Luyten FP. A scientific basis for the biologic regeneration of synovial joints. [Review] [169 refs]. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1997; 83:167-169.
5. An YH, Friedman RJ, Draughn RA. Animal models of fracture or osteotomy. In: An YH, Friedman RJ (eds) Animal models in orthopaedic research. CRC Press, Boca Raton; 1999:197-217.
6. Harvinder SS, Kanim LEA, Girardi F, Cammisa FP, Dawson ED. Animal models of spinal instability and spinal fusion. In: An YH, Friedman RJ (eds) Animal models in orthopaedic research. CRC Press, Boca Raton; 1999:505-526.
7. Lind M, Song Y, Goodman SB. Animal models for investigations of biomaterial debris. In: An YH, Friedman RJ (eds) Animal models in orthopaedic research. CRC Press, Boca Raton; 1999:427-441.
8. Cremieux AC, Carbon C. Experimental models of bone and prosthetic joint infections. [Review] [64 refs]. Clin Infect Dis 1997; 25:1295-1302.
9. An YH, Friedman RJ. Animal models of orthopaedic prosthetic infection. In: An YH, Friedman RJ (eds) Animal models in orthopaedic research. CRC Press, Boca Raton; 1999:443-457.
10. Sumner DR, Galante JO. Bone ingrowth. In: Evarts CM (ed) Surgery of the musculoskeletal system. Churchill Livingstone, New York; 1990:151-176.
11. Sumner DR. Bone ingrowth implications for establishment and maintenance of cementless porous-coated interfaces. In: Callaghan JJ, Dennis DA, Paprosky WGand Rosenberg AG (eds) Orthopaedic knowledge update: hip and knee reconstruction. American Academy of Orthopaedic Surgeons, Rosemont, Illinois; 1995:57-68.
12. Jacobs JJ, Goodman SB, Sumner DR, Hallab NJ. Biological response to orthopaedic implants. In: Anonymous Orthopaedic Basic Science. American Academy of Orthopaedic Surgeons, Rosemont, Illinois; 2000:401-426.
13. Branemark PI, Breine U, Johansson B, Roylance PJ, Röckert H, Yoffey JM. Regeneration of bone marrow. Acta Anat 1964; 59:1-46.
14. Sumner DR, Kienapfel H, Galante JO. Metallic implants. In: Habal MB, Reddi AH (eds) Bone Grafts & Bone Substitutes. W.B. Saunders Company, Philadelphia; 1992:252-262.
15. Callaghan JJ. The clinical results and basic science of total hip arthroplasty with porous-coated prostheses. J Bone Joint Surg Am 1993; 75-A:299-310.
16. Kienapfel H, Griss P. Fixation by ingrowth. In: Callaghan JJ, Rosenberg AGand Rubash H (eds) The Adult Hip. Lippincott-Raven, Philadelphia; 1998:201-209.
17. Pilliar RM. Porous-surfaced metallic implants for orthopedic applications. J Biomed Mater Res 1987; 21(A1):1
18. Kienapfel H, Sprey C, Wilke A and Griss P. Implant fixation by bone ingrowth. [Review] [146 refs]. J Arthrop 1999; 14:355-368.
19. Sumner DR, Turner TM, Urban RM. Animal models of bone ingrowth and joint replacement. In: An YH, Friedman RJ (eds) Animals Models in Orthopedic Research. CRC Press, Boca Raton, Fla; 1999:407-425.
20. Sumner DR. Bone remodeling of the proximal femur. In: Callaghan JJ, Rosenberg AGand Rubash H (eds) The adult hip. Lippincott-Raven Publishers, New York; 1998:211-216.
21. Tagil M, Jeppsson C, Aspenberg P. Bone graft incorporation. Effects of osteogenic protein-1 and impaction. Clin Orthop 2000; 371:240-245.
22. Lamerigts NM, Buma P, Aspenberg P, Schreurs BW, Slooff TJ. Role of growth factors in the incorporation of unloaded bone allografts in the goat. Clin Orthop 1999; 368:260-270.
23. Goodman SB, Song Y, Chun L, Regula D, Aspenberg P. Effects of TGFbeta on bone ingrowth in the presence of polyethylene particles. J Bone Joint Surg Br 1999; 81:1069-1075.
24. Winet H, Bao JY. Fibroblast growth factor-2 alters the effect of eroding polylactide-polyglycolide on osteogenesis in the bone chamber. J Biomed Mater Res 1998; 40:567-576.
25. Winet H, Bao JY, Moffat R. Neo-osteogenesis of Haversian trabeculae through a bone chamber implanted in a rabbit tibial cortex: a control model. Calcif Tissue Int 1990; 47:24-34.

26. Aufdemorte TB, Fox WC, Holt GR, McGuff HS, Ammann AJ, Beck LS. An intraosseous device for studies of bone-healing: the effect of transforming growth-factor beta. J Bone Joint Surg Am 1992; 74-A:1153-1161.
27. Soballe K, Hansen ES, B-Rasmussen H, Jorgensen PH, Bünger C. Tissue ingrowth into titanium and hydroxyapatite-coated implants during stable and unstable mechanical conditions. J Orthop Res 1992; 10:285-299.
28. Lind M, Overgaard S, Ongpipattanakul B, Nguyen T, Bünger C, Sobelle K. Transforming growth factor-b1 stimulates bone ongrowth to weight-loaded tricalcium phosphate-coated implants. J Bone Joint Surg [Br] 1996; 78-B:377-382.
29. Bragdon CR, Burke D, Lowenstein JD, O'Connor DO, Ramamurti B, Jasty M, Harris WH. Differences in stiffness of the interface between a cementless porous implant and cancellous bone in vivo in dogs due to varying amounts of implant motion. J Arthrop 1996; 11:945-951.
30. Howie DW, Vernon-Roberts B, Oakeshott R, Manthey B. A rat model of resorption in bone at the cement-bone interface in the presence of polyethylene wear particles. J Bone Joint Surg Am 1988; 70-A:257-263.
31. Bobyn JD, Jacobs JJ, Tanzer M, Urban RM, Aribindi R, Sumner DR, Turner TM, Brook CE. The susceptibility of smooth implant surfaces to periimplant fibrosis and migration of polyethylene wear debris. Clin Orthop 1995; 311:21-39.
32. Prendergast PJ, Huiskes R, Soballe K. Biophysical stimuli on cells during tissue differentiation at implant interfaces. J Biomech 1997; 30:539-548.
33. Andersson GBJ, Gaechter A, Galante JO, Rostoker W. Segmental replacement of long bones in baboons using a fiber titanium implant. J Bone Joint Surg Am 1978; 60-A:31-40.
34 . Virolainen P, Inoue N, Nagao M, Ohnishi I, Frassica F, Chao EY. Autogenous onlay grafting for enhancement of extracortical tissue formation over porous-coated segmental replacement prostheses. J Bone Joint Surg Am 1999; 81:493-499.
35. Heck DA, Nakajima I, Kelly PJ, Chao EY. The effect of load alteration on the biological and biomechanical performance of a titanium fiber-metal segmental prosthesis. J Bone Joint Surg Am 1986; 68-A:118-126.
36. Turner TM, Urban RM, Sumner DR, Galante JO. Revision, without cement, of aseptically loose, cemented total hip prostheses: quantitative comparison of the effects of four types of medullary treatment on bone ingrowth in a canine model. J Bone Joint Surg Am 1993; 75-A:845-862.
37. Sumner DR, Bryan JM, Urban RM, Kuszak JR. Measuring the volume fraction of bone ingrowth: a comparison of three techniques. J Orthop Res 1990; 8:448-452.
38. Soballe K, Hansen ES, Brockstedt-Rasmussen H, Bünger C. Hydroxyapatite coating converts fibrous tissue to bone around loaded implants. J Bone Joint Surg Br 1993; 75-B:270-278.
39. Burr DB, Mori S, Boyd RD, Sun TC, Blaha JD, Lane L, Parr J. Histomorphometric assessment of the mechanisms for rapid ingrowth of bone to HA/TCP coated implants. J Biomed Mater Res 1993; 27:645-653.
40. Sumner DR, Turner TM, Purchio AF, Gombotz WR, Urban RM, Galante JO. Enhancement of bone ingrowth by transforming growth factor beta. J Bone Joint Surg [Am] 1995; 77-A:1135-1147.
41. Turner TM, Sumner DR, Urban RM, Galante JO. Maintenance of proximal cortical bone with use of a less stiff femoral component in hemiarthroplasty of the hip without cement. J Bone Joint Surg Am 1997; 79-A:1381-1390.
42. Berzins A, Sumner DR. Implant pushout and pullout tests. In: An YH, Draughn RA (eds) Mechanical testing of bone and the bone-implant interface. CRC Press, Boca Raton; 2000:463-476.
43. Berzins A, Sumner DR. In vitro measurements of implant stability. In: An YH, Draughn RA (eds) Mechanical testing of bone and the bone-implant interface. CRC Press, Boca Raton; 2000:515-526.
44. Cook SD, Anderson RC, Weinstein AM, Skinner HB, Haubold A, Yapp R. An evaluation of LTI carbon and porous titanium hip prostheses. In: Ducheyne P, Van der Perre G, Aubert AE (eds) Biomaterials and Biomechanics. Elsevier Science Publishers B.V.: Amsterdam, 1984:31-36.
45. Cook SD, Thomas KA, Kester MA. Wear characteristics of the canine acetabulum against different femoral prostheses. J Bone Joint Surg Br 1989; 71-B:189-197.
46. Cruess RL, Kwok DC, Duc PN, LeCavalier MA, Dang G-T. The response of articular cartilage to weight-bearing against metal. J Bone Joint Surg Br 1984; 66-B:592-597.
47. Lade R, Sauer B, Doerre E. Long-term perfomance of high purity aluminum oxide ceramic heads in canine endoprosthetic hip replacement. In: Vincenzini P (ed) Ceramics in Surgery. Elsevier Scientific Publishing Company, Amsterdam; 1983:277-286.
48. Yee AJ, Binnington AG, Hearn T, Protzner K, Fornasier VL, Davey JR. Use of a polyglycolide lactide cement plug restrictor in total hip arthroplasty. Clin Orthop 1999; 364:254-266.
49. Breusch SJ, Reitzel T, Schneider U, Volkmann M, Ewerbeck V, Lukoschek M. [Cemented hip prosthesis implanta-tion-decreasing the rate of fat embolism with pulsed pressure lavage]. [German]. Orthopade 2000; 29:578-586.
50. Szucs G, Miko I, Ajzner E, Poti L, Szepesi K, Furka I. Efficacy of prevention of thromboembolic complications with LMW-heparin in experiment. Acta Chir Hung 1997; 36:356-358.
51. Gitelis S, Chen P-Q, Andersson GBJ, Galante JO, Rostoker W, Andriacchi TP. The influence of early

weight-bearing on experimental total hip arthroplasties in dogs. Clin Orthop 1982; 169:291-302.
52. Lord GA, Hardy JR, Kummer FJ. An uncemented total hip replacement: experimental study and review of 300 madreporique arthroplasties. Clin Orthop 1979; 141:2-16.
53. Claes L, Burri C, Neugebauer R, Gruber U. Experimental investigations on hip prostheses with carbon fibre reinforced carbon shafts and ceramic heads. In: Vincenzini P (ed) Ceramics in Surgery. Elsevier Scientific Publishing Company, Amsterdam; 1983:243-250.
54. Ducheyne P, Martens M, Burssens A. Materials, clinical and morphological evaluation of custom-made bioreactive-glass-coated canine hip prostheses. J Biomed Mater Res 1984; 18:1017-1030.
55. Clarke IC, Phillips W, McKellop H, Coster IR, Hedley A, Amstutz HC. Development of a ceramic surface replacement for the hip. An experimental Sialon model. Biomat Med Dev Art Org 1979; 7:111-126.
56. Hori RY, Lewis JL. Mechanical properties of the fibrous tissue found at the bone- cement interface following total joint replacement. J Biomed Mater Res 1982; 16:911-927.
57. Bobyn JD, Cameron HU, Abdulla D, Pilliar RM, Weatherly GC. Biologic fixation and bone modeling with an unconstrained canine total knee prosthesis. Clin Orthop 1982; 166:301-312.
58. Turner TM, Urban RM, Sumner DR, Skipor AK, Galante JO. Bone ingrowth into the tibial component of a canine total condylar knee replacement prosthesis. J Orthop Res 1989; 7:893-901.
59. Walker PS, Rodger RF, Miegel RE, Schiller AL, Deland JT, Robertson DO. An investigation of a compliant interface for press-fit joint replacement. J Orthop Res 1990; 8:453-463.
60. Stulberg BN, Watson JT, Stulberg SD, Bauer TW, Manley MT. A new model to assess tibial fixation in knee arthroplasty. I. Histologic and roentgenographic results. Clin Orthop 1991; 263:288-302.
61. Sumner DR, Berzins A, Turner TM, Igloria R, Natarajan R. Initial in vitro stability of the tibial component in a canine model of cementless total knee replacement. J Biomech 1994; 27:929-939.
62. Sumner DR, Turner TM, Dawson D, Rosenberg AG, Urban RM, Galante JO. Effect of pegs and screws on bone ingrowth in cementless total knee arthroplasty. Clin Orthop 1994; 309:150-155.
63. Bellemans J. Osseointegration in porous-coated knee arthroplasty. The influence of component coating type in sheep. Acta Orthop Scand 1999; (Suppl) 288:1-35.
64. Matthews LS, Goldstein SA. The prosthesis-bone interface in total knee arthroplasty. Clin Orthop 1992; 276:50-55.
65. van Loon CJ, de Waal M, Buma P, Stolk T, Verdonschot N, Tromp AM, Huiskes R, Barneveld A. Autologous morsellised bone grafting restores uncontained femoral bone defects in knee arthroplasty. An in vivo study in horses. J Bone Joint Surg Br 2000; 82:436-444.
66. LaBerge M, Bobyn JD, Drouin G, Rivard CH. Evaluation of metallic personalized hemiarthroplasty: a canine patellofemoral model. J Biomed Mater Res 1992; 26:239-254.
67. Markel DC, Femino JE, Farkas P, Markel SF. Analysis of lower extremity embolic material after total knee arthroplasty in a canine model. J Arthrop 1999; 14:227-232.
68. Curtin WA, Wang GJ, Goodman NC, Abbott RD, Spotnitz WD. Reduction of hemorrhage after knee arthroplasty using cryo-based fibrin sealant. J Arthrop 1999; 14:481-487.
69. Sacomen D, Smith RL, Song Y, Fornasier V, Goodman SB. Effects of polyethylene particles on tissue surrounding knee arthroplasties in rabbits. J Biomed Mater Res 1998; 43:123-130.
70. Belmatoug N, Cremieux AC, Bleton R, Volk A, Saleh-Mghir A, Grossin M, Gurry L, Carbon L. A new model of experimental prosthetic joint infection due to methicillin-resistant Staphylo-coccus aureus: a microbiologic, histopathologic, and magnetic resonance imaging characterization. J Infect Dis 1996; 174:414-417.
71. Chang YS, Gu HO, Kobayashi M, Oka M. Influence of various structure treatments on histological fixation of titanium implants. J Arthrop 1998; 13:816-825.
72. Hamadouche M, Meunier A, Greenspan DC, Blanchat C, Zhong JP, La Torre GP, Sedel L. Bioactivity of sol-gel bioactive glass coated alumina implants. J Biomed Mater Res 2000; 52:422-429.
73. Vercaigne S, Wolke JG, Naert I, Jansen JA. The effect of titanium plasma-sprayed implants on trabecular bone healing in the goat. Biomaterials 1998; 19:1093-1099.
74. Kato H, Nakamura T, Nishiguchi S, Matsusue Y, Kobayashi M, Miyiazaki T, Kim HM, Kokubo T. Bonding of alkali- and heat-treated tantalum implants to bone. J Biomed Mater Res 2000; 53:28-35.
75. Rahal MD, Delorme D, Branemark PI, Osmond DG. Myelointegration of titanium implants: B lymphopoiesis and hemopoietic cell proliferation in mouse bone marrow exposed to titanium implants. Int J Oral Maxillofac Implants 2000; 15:175-184.
76. Sovak G, Weiss A, Gotman I. Osseointegration of Ti6Al4V alloy implants coated with titanium nitride by a new method. J Bone Joint Surg Br 2000; 82:290-296.
77. Ferris DM, Moodie GD, Dimond PM, Gioranni CW, Ehrlich MG, Valentini RF. RGD-coated titanium implants stimulate increased bone formation in vivo. Biomaterials 1999; 20:2323-2331.
78. Nishiguchi S, Kato H, Fujita H, Kim HM, Miyaji F, Kokubo T, Nakamura T. Enhancement of bone-bonding strengths of titanium alloy implants by alkali and heat treatments. J Biomed Mater Res 1999; 48:689-696.
79. Guglielmotti MB, Renou S, Cabrini RL. A histo-morphometric study of tissue interface by laminar implant

test in rats. Int J Oral Maxillofac Implants 1999; 14:565-570.
80. Hayashi K, Mashima T, Uenoyama K. The effect of hydroxyapatite coating on bony ingrowth into grooved titanium implants. Biomaterials 1999; 20:111-119.
81. Bobyn JD, Stackpool GJ, Hacking SA, Tanzer M, Krygier JJ. Characteristics of bone ingrowth and interface mechanics of a new porous tantalum biomaterial. J Bone Joint Surg Br 1999; 81:907-914.
82. Lopez-Sastre S, Gonzalo-Orden JM, Altonaga JA, Altonaga JR, Orden MA. Coating titanium implants with bioglass and with hydroxyapatite. A comparative study in sheep. Int Orthop 1998; 22:380-383.
83. An YH, Friedman RJ, Jiang M, LaBreck JC, Draughn RA, Butehorn HF 3rd, Bauer TW. Bone ingrowth to implant surfaces in an inflammatory arthritis model. J Orthop Res 1998; 16:576-584.
84. D'Lima DD, Lemperle SM, Chen PC, Holmes RE, Colwell CWJ. Bone response to implant surface morphology. J Arthrop 1998; 13:928-934.
85. Piattelli A, Manzon L, Scarano A, Paolantonio M, Piattelli M. Histologic and histomorphometric analysis of the bone response to machined and sandblasted titanium implants: an experimental study in rabbits. Int J Oral Maxillofac Implants 1998; 13:805-810.
86. Dhert WJ, Thomsen P, Blomgren AK, Esposito M, Ericson LE, Verbout AS. Integration of press-fit implants in cortical bone: a study on interface kinetics. J Biomed Mater Res 1998; 41:574-583.
87. Clemens JA, Klein CP, Vriesde RC, Rozing PM, de Groot K. Healing of large (2 mm) gaps around calcium phosphate-coated bone implants: a study in goats with a follow-up of 6 months. J Biomed Mater Res 1998; 40:341-349.
88. Ito K, Nanba K, Nishida T, Sato H, Murai S. Comparison of osseointegration between hydroxyapatite-coated and uncoated threaded titanium dental implants placed into surgically-created bone defect in rabbit tibia. J Oral Sci 1998; 40:37-41.
89. Pazzaglia UE, Brossa F, Zatti G, Chiesa R, Andrini L. The relevance of hydroxyapatite and spongious titanium coatings in fixation of cementless stems. An experimental comparative study in rat femur employing histological and microangiographic techniques. Arch Orthop Trauma Surg 1998; 117:279-285.
90. Blom EJ, Verheij JG, de Blieck-Hogervorst JM, Di S, Klein CP. Cortical bone ingrowth in growth hormone-loaded grooved implants with calcium phosphate coatings in goat femurs. Biomaterials 1998; 19:263-270.
91. Simmons CA, Valiquette N, Pilliar RM. Osseointegration of sintered porous-surfaced and plasma spray-coated implants: An animal model study of early post-implantation healing response and mechanical stability. J Biomed Mater Res 1999; 47:127-138.
92. Li DH, Liu BL, Zou JC, Xu KW. Improvement of osseointegration of titanium dental implants by a modified sandblasting surface treatment: an in vivo interfacial biomechanics study. Implant Dent 1999; 8:289-294.
93. Baker D, London RM, O'Neal R. Rate of pull-out strength gain of dual-etched titanium implants: a comparative study in rabbits. Int J Oral Maxillofac Implants 1999; 14:722-728.
94. Moroni A, Faldini C, Chilo V, Rocca M, Stea S, Giannini S. The effect of surface material and roughness on bone screw stability. J Orthop Trauma 1999; 13:477-482.
95. Wang J, Yang R, Gerstenfeld LC, Glimcher MJ. Characterization of demineralized bone matrix-induced osteogenesis in rat calvarial bone defects: III. Gene and protein expression. Calcif Tissue Int 2000; 67:314-320.
96. Yoshikawa T, Ohgushi H, Akahane M, Tamai S, Ichijima K. Analysis of gene expression in osteogenic cultured marrow/hydroxyapatite construct implanted at ectopic sites: a comparison with the osteogenic ability of cancellous bone. J Biomed Mater Res 1998; 41:568-573.
97. Lafont J, Baroukh B, Berdal A, Colombier ML, Barritault D, Caruelle JP, Saffar JL. RGTA11, a new healing agent, triggers developmental events during healing of cranio-tomy defects in adult rats. Growth Factors 1998; 16:23-38.
98. Chang BS, Lee CK, Hong KS, Youn HJ, Ryu HS, Chung SS, Park KW. Osteoconduction at porous hydroxyapatite with various pore configurations. Biomaterials 2000; 21(12):1291-1298.
99. Yuan H, Li Y, de Bruijn JD, de Groot K, Zhang X. Tissue responses of calcium phosphate cement: a study in dogs. Biomaterials 2000; 21:1283-1290.
100. Lind M, Overgaard S, Song Y, Goodman SB, Bunger C, Sobolle K. Osteogenic protein 1 device stimulates bone healing to hydroxyapaptite-coated and titanium implants. J Arthrop 2000; 15:339-346.
101. Lewandrowski KU, Gresser JD, Wise DL, Trantol DJ. Bioresorbable bone graft substitutes of different osteoconductivities: a histologic evaluation of osteointegration of poly(propylene glycol-co-fumaric acid)-based cement implants in rats. Biomaterials 2000; 21:757-764.
102. Frayssinet P, Mathon D, Lerch A, Autefage A, Collard P, Rouquet N. Osseointegration of composite calcium phosphate bioceramics. J Biomed Mater Res 2000; 50:125-130.
103. Meraw SJ, Reeve CM, Lohse CM, Sioussat TM. Treatment of peri-implant defects with combination growth factor cement. J Periodontol 2000; 71:8-13.
104. Wheeler DL, Eschbach EJ, Hoellrich RG, Montfort MJ, Chamberland DL. Assessment of resorbable bioactive material for grafting of critical-size cancellous defects. J Orthop Res 2000; 18:140-148.
105. Kon E, Muraglia A, Corsi A, Bianco P, Marcacci M, Martin I, Boyde A, Ruspantini I, Chistolini P, Rocca M, Giardino R, Cancedda R, Quarto R. Autologous bone marrow stromal cells loaded onto porous hydroxyapatite ceramic accelerate bone repair in critical-size defects of sheep long bones. J Biomed Mater Res 2000; 49:328-

337.
106. Bessho K, Carnes DL, Cavin R, Chen HY, Ong JL. BMP stimulation of bone response adjacent to titanium implants in vivo. Clin Oral Implants Res 1999; 10:212-218.
107. Anselme K, Noel B, Flautre B, Blary MC, Delecourt C, Decsames M, Hardoyin P. Association of porous hydroxyapatite and bone marrow cells for bone regeneration. Bone 1999; 25:51S-54S.
108. Laffargue P, Hildebrand HF, Rtaimate M, Frayssinet P, Amoureux JP, Marchandise X. Evaluation of human recombinant bone morphogenetic protein-2-loaded tricalcium phosphate implants in rabbits' bone defects. Bone 1999; 25:55S-58S.
109. Rodeo SA, Suzuki K, Deng XH, Wozney J, Warren RF. Use of recombinant human bone morphogenetic protein-2 to enhance tendon healing in a bone tunnel. Am J Sports Med 1999; 27:476-488.
110. Cochran DL, Schenk R, Buser D, Wozney JM, Jones AA. Recombinant human bone morphogenetic protein-2 stimulation of bone formation around endosseous dental implants. J Periodontol 1999; 70:139-150.
111. Meraw SJ, Reeve CM, Wollan PC. Use of alendronate in peri-implant defect regeneration. J Periodontol 1999; 70:151-158.
112. Sato S, Koshino T, Saito T. Osteogenic response of rabbit tibia to hydroxyapatite particle-Plaster of Paris mixture. Biomaterials 1998; 19:1895-1900.
113. Koempel JA, Patt BS, O'Grady K, Wozney J, Toriumi DM. The effect of recombinant human bone morphogenetic protein-2 on the integration of porous hydroxyapatite implants with bone. J Biomed Mater Res 1998; 41:359-363.
114. Guicheux J, Gauthier O, Aguado E, Pilet P, Couillaud S, Jegou D, Daculsi G. Human growth hormone locally released in bone sites by calcium-phosphate biomaterial stimulates ceramic bone substitution without systemic effects: a rabbit study. J Bone Miner Res 1998; 13:739-748.
115. Sumner DR, Turner TM, Urban RM, Leven RM, Hawkins M, Nichols EH, McPherson JM, Galante JO. Locally delivered rhTGF-β_2 enhances bone ingrowth and bone regeneration at local and remote sites of skeletal injury. J Orthop Res 2001; 19:85-94.
116. Muzzarelli RAA, Ramos V, Stanic V, Dubini B, Mattiolibelmonte M, Tosi G, Giardino R. Osteogenesis promoted by calcium phosphate N, N-dicarboxymethly chitosan. Carbohydrate Polymers 1998; 36(4):267-276.
117. Hong L, Tabata Y, Yamamoto M, Miyamoto S, Yamada K, Hashimoto N, Ikada Y. Comparison of bone regeneration in a rabbit skull defect by recombinant human BMP-2 incorporated in biodegradable hydrogel and in solution. Journal of Biomaterials Science, Polymer Edition 1998; 9:1001-1014.
118. Tabata Y, Yamada K, Miyamoto S, Nagata I, Kikuchi H, Aoyama I, Tamura, Ikada Y. Bone regeneration by basic fibroblast growth factor complexed with biodegradable hydrogels. Biomaterials 1998; 19(7-9):807-815.
119. Zellin G, Beck S, Hardwick R, Linde A. Opposite effects of recombinant human transforming growth factor-beta-1 on bone regeneration in vivo - effects of exclusion of periosteal cells by microporous membrane. Bone 1998; 22:613-620.
120. Constantz BR, Barr BM, Ison IC, Fulmer MT, Baker J, McKinney L, Goodman SB, Gunasekaren S, Delaney DC, Ross J, Poser Rd. Histological, chemical, and crystallographic analy-sis of four calcium phosphate cements in different rab-bit osseous sites. J Biomed Mater Res 1998; 43:451-461.
121. Kawamura H, Ito A, Miyakawa S, Layrolle P, Ojima K, Ichinose N, Tateishi T. Stimulatory effect of zinc-releasing calcium phosphate implant on bone formation in rabbit femora. J Biomed Mater Res 2000; 50:184-190.
122. Mori M, Isobe M, Yamazaki Y, Ishihara K, Nakabayashi N. Restoration of segmental bone defects in rabbit radius by biodegradable capsules containing recombinant human bone morphogenetic protein-2. J Biomed Mater Res 2000; 50:191-198.
123. Green JR, Nemzek JA, Arnoczky SP, Johnson LL, Balas MS. The effect of bone compaction on early fixation of porous-coated implants. J Arthrop 1999; 14:91-97.
124. Yaylaoglu MB, Korkusuz P, Ors U, Korkusuz F, Hasirci V. Development of a calcium phosphate-gelatin composite as a bone substitute and its use in drug release. Biomaterials 1999; 20:711-719.
125. Gauthier O, Bouler JM, Weiss P, Bosco J, Daculsi G, Aguado E. Kinetic study of bone ingrowth and ceramic resorption associated with the implantation of different injectable calcium-phosphate bone substitutes. J Biomed Mater Res 1999; 47:28-35.
126. Gauthier O, Bouler JM, Aguado E, Pilet P, Daculsi G. Macroporous biphasic calcium phosphate ceramics: influence of macropore diameter and macroporosity percentage on bone ingrowth. Biomaterials 1998; 19:133-139.
127. Pan J, Shirota T, Ohno K, Michi K. Effect of ovariectomy on bone remodeling adjacent to hydroxyapatite-coated implants in the tibia of mature rats. J Oral Maxillofac Surg 2000; 58:877-882.
128. McCracken M, Lemons JE, Rahemtulla F, Prince CW, Feldman D. Bone response to titanium alloy implants placed in diabetic rats. Int J Oral Maxillofac Implants 2000; 15:345-354.
129. Nociti FHJ, Sallum EA, Toledo S, Newman HN, Sallum AW. Effect of calcitonin on bone healing following titanium implant insertion. J Oral Sci 1999; 41:77-80.
130. Motohashi M, Shirota T, Tokugawa Y, Ohno K, Michi K, Yamaguchi A. Bone reactions around hydroxyapatite-coated implants in ovariectomized rats. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999; 87(2):145-152.
131. Amstutz HC, Kim WC, O'Carroll PF, Kabo JM. Canine porous resurfacing hip arthroplasty. Clin Orthop 1986; 207:270-289.

132. Chen P-Q, Turner TM, Ronningen H, Galante J, Urban R, Rostoker W. A canine cementless total hip prosthesis model. Clin Orthop 1983; 176:24-33.
133. Dai KR, Liu YK, Park JB, Clark CR, Nishiyama K, Zheng ZK. Bone-particle-impregnated bone cement: An in vivo weight-bearing study. J Biomed Mater Res 1991; 25:141-156.
134. Walenciak MT, Zimmerman MC, Harten RD, Ricci JL, Stamer DT. Biomechanical and histological analysis of an HA coated, arc deposited CPTi canine hip prosthesis. J Biomed Mater Res 1996; 31:465-474.
135. Plenk H, Jr., Pflüger G, Böhler N, Gottsauner-Wolf F, Grundschober F, Schider S. Long-term anchorage of cementless tantalum and niobium femoral stems in canine hip-joint replacement. In: Ducheyne P, Van der Perre Gand Aubert AE (eds) Biomaterials and Biomechanics. Elsevier Science Publishers B.V., Amsterdam; 1984:61-66.
136. Finkelstein JA, Anderson GI, Waddell JP, Richards RR, Hearn TC, Schemitsch E. A study of micromotion and appositional bone growth to a canine madreporic-surfaced femoral component. J Arthrop 1994; 9:317-324.
137. Maistrelli GL, Fornasier V, Binnington A, McKenzie K, Sessa V, Harrington I. Effect of stem modulus in a total hip arthroplasty model. J Bone Joint Surg [Br] 1991; 73-B:43-46.
138. Radin EL, Rubin CT, Thrasher EL, Lanyon LE, Crugnola AM, Schiller AS, Paul IL, Rose RM. Changes in the bone-cement interface after total hip replacement. J Bone Joint Surg Am 1982; 64-A:1188-1200.
139. Gavens AJ, Beals NB, DeMane MF, Davidson JA, Roberson JR, Heyligers I, Miller M, Spector M. Porous polysulfone coated femoral stems. In: de Putter C, de Lange GL, de Groot Kand Lee AJC (eds) Implant Materials in Biofunction. Elsevier Science Publishers B.V., Amsterdam; 1988:159-164.
140. Thomas KA, Cook SD, Haddad RJ, Kay JF, Jarcho M. Biologic response to hydroxyapatite-coated titanium hips: a preliminary study in dogs. J Arthrop 1989; 4:43-53.
141. Sumner DR, Galante JO. Determinants of stress shielding: design vs materials vs interface. Clin Orthop 1992; 274:202-212.
142. Richards RR, Minas T, Johnston DWC, Waddell JP. Biologic response to uncemented madreporic canine hip arthroplasty. Can J Surg 1987; 30:245-248.
143. Thornhill TS, Ozuna RM, Shortkroff S, Keller K, Sledge CB, Spector M. Biochemical and histological evaluation of the synovial-like tissue around failed (loose) total joint replacement prostheses in human subjects and a canine model. Biomaterials 1990; 11:69-72.
144. Roberson JR, Spector M, Baggett MA, Kita K. Porous-coated femoral components in a canine model for revision arthroplasty. J Bone Joint Surg Am 1988; 70-A:1201-1207.
145. Ronningen H, Lereim P, Galante J, Rostoker W, Turner TM, Urban R. Total surface hip arthroplasty in dogs using a fiber metal composite as a fixation method. J Biomed Mater Res 1983; 17:643-653.
146. Turner TM, Sumner DR, Urban RM, Rivero DP, Galante JO. A comparative study of porous coatings in a weight-bearing total hip-arthroplasty model. J Bone Joint Surg Am 1986; 68-A:1396-1409.
147. Russotti GM, Okada Y, Fitzgerald RH, Chao EYS, Gorski JP. Efficacy of using a bone graft substitute to enhance biological fixation of a porous metal femoral component. In: Brand RA (ed) The Hip. C.V. Mosby, St. Louis; 1987:120-154.
148. Paul HA, Bargar WL. Histologic changes in the dog femur following total hip replacement with current cementing techniques. J Arthrop 1986; 1:5-9.
149. Vanderby R, Jr., Manley PA, Kohles SS, McBeath AA. Fixation stability of femoral components in a canine hip replacement model. J Orthop Res 1992; 10:300-309.
150. Sumner DR, Turner TM, Urban RM, Galante JO. Remodeling and ingrowth of bone at two years in a canine cementless total hip-arthroplasty model. J Bone Joint Surg Am 1992; 74-A:239-250.
151. Greis PE, Kang JD, Silvaggio V, Rubash HE. A long-term study on defect filling and bone ingrowth using a canine fiber metal total hip model. Clin Orthop 1992; 274:47-59.
152. Griss P, Greenspan DC, Heimke G, Krempien B, Buchinger R, Hench LL, Jentschura G. Evaluation of a bioglass-coated Al2O3 total hip prosthesis in sheep. J Biomed Mater Res Symposium 1976; 7:511-518.
153. Griss P, Silber R, Merkle B, Haehner K, Heimke G, Krempien B. Biomechanically induced tissue reactions after Al2O3-ceramic hip joint replacement. Experimental and early clinical results. J Biomed Mater Res Symposium 1976; 7:519-528.
154. Harris WH, Jasty M. Bone ingrowth into porous coated canine acetabular replacements: the effect of pore size, apposition, and dislocation. In: Fitzgerald RH (ed) The Hip. C.V. Mosby, St. Louis; 1985:214-234.
155. Hedley AK, Clarke IC, Kozinn SC, Coster I, Gruen T, Amstutz HC. Porous-ingrowth fixation of the femoral compo-nent in a canine surface replacement of the hip. Clin Orthop 1982; 163:300-311.
156. Hedley AK, Kabo M, Kim W, Coster I, Amstutz HC. Bony ingrowth fixation of newly designed acetabular components in a canine model. Clin Orthop 1983; 176:12-23.
157. Heiner JP, Manley P, Kohles S, Ulm M, Bogart L, Vanderby R JR. Ingrowth reduces implant-to-bone relative displace-ments in canine acetabular prostheses. J Orthop Res 1994; 12:657-664.
158. Itami Y, Akamatsu N, Tomita Y, Nagai M. A cement-less system of total hip prosthesis: experimental studies on total hip prosthesis in dogs. Arch Orthop Trauma Surg 1982; 100:183-189.
159. Jasty M, Bragdon CR, Haire T, Mulroy RD, Harris WH. Comparison of bone ingrowth into cobalt chrome

sphere and titanium fiber mesh porous coated cementless canine acetabular components. J Biomed Mater Res 1993; 27:639-644.
160. Jasty M, Bragdon CR, Rubash H, Schutzer SF, Haire T, Harris W. Unrecognized femoral fractures during cement-less total hip arthroplasty in the dog and their effect on bone ingrowth. J Arthrop 1992; 7:501-508.
161. Jasty M, Rubash HE, Paiement GD, Bragdon CR, Parr J, Harris WH. Porous-coated uncemented components in experi-mental total hip arthroplasty in dogs. Clin Orthop 1992; 280:300-309.
162. Kang JD, McKernan DJ, Kruger M, Mutschler T, Thompson WH, Rubash HE. Ingrowth and formation of bone in defects in an uncemented fiber-metal total hip-replacement model in dogs. J Bone Joint Surg Am 1991; 73-A(1):93-105.
163. Lembert E, Galante J, Rostoker W. Fixation of skeletal replacement by fiber metal composites. Clin Orthop 1972; 87:303-310.
164. Maistrelli GL, Mahomed N, Fornasier V, Antonelli L, Li Y, Binnington A. Functional osseointegration of hydroxyapatite-coated implants in a weight-bearing canine model. J Arthrop 1993; 8:549-554.
165. Manley PA, Vanderby R, Kohles S, Markel MD, Heiner JP. Alterations in femoral strain, micromotion, cortical geometry, cortical porosity, and bony ingrowth in uncemented collared and collarless prostheses in the dog. J Arthrop 1995; 10:63-73.
166. McDonald DJ, Fitzgerald RH, Chao EYS. The enhancement of fixation of a porous-coated femoral component by autograft and allograft in the dog. J Bone Joint Surg Am 1988; 70-A:729
167. Mendes DG, Walker PS, Figarola F, Bullough PG. Total surface hip replacement in the dog. Clin Orthop 1974; 100:256-264.
168. DeYoung DJ, Schiller RA. Radiographic criteria for evaluation of uncemented total hip replacement in dogs. Veter Surg 1992; 21:88-98.
169. Jasty M, Bragdon CR, Zalenski E, O'Connor D, Page A, Harris WH. Enhanced stability of uncemented canine femoral components by bone ingrowth into the porous coatings. J Arthrop 1997; 12:106-113.
170. Magee FP, Weinstein AM, Longo JA, Koeneman JB, Yapp RA. A canine composite femoral stem. Clin Orthop 1988; 235:237-252.
171. Sumner DR, Turner TM, Igloria R, Urban RM, Galante JO. Trabecular bone functional adaptation and bone ingrowth vary as a function of implant stiffness. J Biomech 1998; 31:909-917.
172. van Rietbergen B, Huiskes R, Weinans H, Sumner DR, Turner TM, Galante JO. The mechanism of bone remodeling and resorption around press-fitted THA stems. J Biomech 1993; 26:369-382.
173. Cheng SL, Davey JR, Inman RD, Binnington AG, Smith TJ. The effect of the medial collar in total hip arthroplasty with porous-coated components inserted without cement. J Bone Joint Surg Am 1995; 77-A:118-123.
174. Schreurs BW, Huiskes R, Buma P, Sloof TJ. Biomechanical and histological evaluation of a hydroxyapatite-coated titanium femoral stem fixed with an intramedullary morsellized bone grafting technique: an animal experiment on goats. Biomaterials 1996; 17:1177-1186.
175. Munting E. The contributions and limitations of hydroxyapatite coatings to implant fixation: a histo-morphometric study of load bearing implants in dogs. Int Orthop 1996; 20:1-6.
176. Dowd JE, Schwendeman LJ, Macaulay W, Doyle JS, Shanbhag AS, Wilson S, Herndon JH, Rubash HE. Aseptic loosening in uncemented total hip arthroplasty in a canine model. Clin Orthop 1995; 319:106-121.
177. Schiller TD, DeYoung DJ, Schiller RA, Aberman HA, Hungerford DS. Quantitative ingrowth analysis of a porous-coated acetabular component in a canine model. Veter Surg 1993; 22:276-280.
178. Spector M, Shortkroff S, Hsu HP, Lane N, Sledge CB, Thornhill TS. Tissue changes around loose prostheses. A canine model to investigate the effects of an anti-inflammatory agent. Clin Orthop 1990; 261:140-140.
179. Phillips TW, Gurr KR, Rao DR. Hip implant evaluation in an arthritic animal model. Arch Orthop Trauma Surg 1990; 109:194-196.
180. Parvongnukul K, Lumb WV. Evaluation of polytetra-fluoroethylene-graphite-coated total hip prostheses in goats. Am J Vet Res 1978; 39:221-228.
181. Esslinger JO, Rutkowski EJ. Studies on the skeletal attachment of experimental hip prostheses in the pygmy goat and the dog. J Biomed Mater Res 1973; 7:187-193.
182. Kraemer WJ, Maistrelli GL, Fornasier V, Binnington A, Zhao JF. Migration of polyethylene wear debris in hip arthroplasties: a canine model. J Appl Biomater 1995; 6:225-230.
183. Oates KM, Barrera DL, Tucker WN, Chau CC, Bugbee WD, Convery FR. In vivo effect of pressurization of polymethyl methacrylate bone-cement. Biomechancial and histo-logic analysis. J Arthrop 1995; 10:373-381.
184. Otsuka NY, Binnington AG, Fornasier VL, Davey JR. Fixation with biodegradable devices of acetabular components in a canine model. Clin Orthop 1994; 306:250-255.
185. Fujita H, Ido K, Matsuda Y, Iida H, Oka M, Kitamura Y, Nakamura T. Evaluation of bioactive bone cement in canine total hip arthroplasty. J Biomed Mater Res 2000; 49:273-288.
186. Bobyn JD, Toh KK, Hacking SA, Tanzer M, Krygier JJ. Tissue response to porous tantalum acetabular cups: a canine model. J Arthrop 1999; 14:347-354.
187. Schimmel JW, Buma P, Versleyen D, Huiskes R, Slooff TJ. Acetabular reconstruction with impacted morselized cancellous allografts in cemented hip arthroplasty: a histological and biomechanical study on the goat. J Arthrop 1998; 13:438-448.

188. Bhumbra RP, Walker PS, Berman AB, Emmanual J, Barrett DS, Blunn GW. Prevention of loosening in total hip replacements using guided bone regeneration. Clin Orthop 2000; 372:192-204.
189. Moroni A, Rocca M, Faldini C, Stea S, Giardino R, Giannini S. Hydroxyapatite fully coated conic hip prosthetic stem: a long term animal study. Annales Chirurgiae et Gynaecologiae 1999; 88:198-204.
190. Hacking SA, Bobyn JD, Tanzer M, Krygier JJ. The osseous response to corundum blasted implant surfaces in a canine hip model. Clin Orthop 1999; 364:240-253.
191. Harvey EJ, Bobyn JD, Tanzer M, Stackpool GJ, Krygier JJ, Hacking SA. Effect of flexibility of the femoral stem on bone-remodeling and fixation of the stem in a canine total hip arthroplasty model without cement. J Bone Joint Surg Am 1999; 81:93-107.
192. Brumby SA, Howie DW, Pearcy MJ, Wang AW, Nawana NS. Radiographic and histologic analysis of cemented double tapered femoral stems. Clin Orthop 1998; 355:229-237.
193. Ferris BD. A quantitative study of the tissue reaction and its relationship to debris production from a joint implant. J Exp Pathol 1990; 71:367-373.
194. Jasty M, Krushell RJ, Zalenski E, O'Connor D, Sedlacek R, Harris W. The contribution of the nonporous distal stem to the stability of proximally porous-coated canine femoral components. J Arthrop 1993; 8:33-41.
195. Litsky AS, Rose RM, Rubin CT, Thrasher EL. A reduced-modulus acrylic bone cement: preliminary results. J Orthop Res 1990; 8:623-626.
196. Szivek JA, Kersey RC, DeYoung DW, Ruth JT. Load transfer through a hydroxyapatite-coated canine hip implant. J Appl Biomater 1994; 5:293-306.
197. Heiner JP, Kohles SS, Manley PA, Vanderby R, Jr., Markel MD. Stability of proximal femoral grafts in canine hip arthroplasty. Clin Orthop 1997; 341:233-240.
198. Rose RM, Martin RB, Orr RB, Radin EL. Architectural changes in the proximal femur following prosthetic insertion: preliminary observations of an animal model. J Biomech 1984; 17:241-249.
199. Weinans H, Huiskes R, van Rietbergen B, Sumner DR, Turner TM, Galante JO. Adaptive bone remodeling around bonded noncemented total hip arthroplasty: a comparison between animal experiments and computer simulation. J Orthop Res 1993; 11:500-513.
200. Bobyn JD, Mortimer ES, Glassman AH, Engh CA, Miller JE, Brooks CE. Producing and avoiding stress shielding: laboratory and clinical observations of noncemented total hip arthroplasty. Clin Orthop 1992; 274:79-96.
201. Bobyn JD, Pilliar RM, Binnington AG, Szivek JA. The effect of proximally and fully porous-coated canine hip stem design on bone modeling. J Orthop Res 1987; 5:393-408.
202. Bouvy BM, Manley PA. Vascular and morphologic changes in canine femora after uncemented hip arthroplasty. Veter Surg 1993; 22:18-26.
203. Finkelstein JA, Anderson GI, Waddell JP, Richards RR, Humeniuk B. A madreporic-surfaced femoral component in a canine total hip arthroplasty model: bone remodelling response at 6 and 24 months. Can J Surg 1995; 38:501-506.
204. Jacobs JJ, Sumner DR, Galante JO. Mechanisms of bone loss associated with total hip replacement. Orthop Clin N Am 1993; 24:583-590.
205. Kohles SS, Vanderby R, Jr., Ashman RB, Manley PA, Markel MD, Heiner JP. Ultrasonically determined elasticity and cortical density in canine femora after hip arthroplasty. J Biomech 1994; 27:137-144.
206. Vanderby R, Jr., Manley PA, Belloli DM, Kohles SS, Thielke RJ, McBeath AA. Femoral strain adaptation after total hip replacement: a comparison of cemented and porous ingrowth components in canines. J Engine Med 1990; 204:97-109.
207. de Waal Malefijt J, Sloof TJ, Huiskes R, de Laat EA, Barentsz JO. Vascular changes following hip arthroplasty. The femur in goats studied with and without cementation. Acta Orthop Scand 1988; 59:643-649.
208. Cook SD, Skinner HB, Weinstein AM, Lavernia CJ, Midgett RJ. The mechanical behavior of normal and osteoporotic canine femora before and after hemiarthroplasty. Clin Orthop 1982; 170:303-312.
209. Lanyon LE, Paul IL, Rubin CT, Thrasher EL, DeLaura R, Rose RM, Radin EL. In vivo strain measurements from bone and prosthesis following total hip replacement. J Bone Joint Surg Am 1981; 63-A:989-1000.
210. Wang X, Shanbhag AS, Rubash HE, Agrawal CM. Short-term effects of bisphosphonates on the biomechanical properties of canine bone. J Biomed Mater Res 1999; 44:456-460.