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# THE EFFECT OF NON INVASIVE LOW INTENSITY PULSED ULTRASOUND ON BONE GROWTH INTO POROUS TANTALUM IMPLANTS

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## ABSTRACT

The purpose of this study was to evaluate the effect of non-invasive, low intensity, pulsed ultrasound on bone growth into tantalum porous implants. Three transcortical cylindrical implants were inserted into both femora of 12 dogs. One leg underwent daily ultrasound stimulation for 40 consecutive minutes with the transducer positioned over the central, or "target" implant, while the contralateral leg served as the control. Six dogs were each treated for periods of two and three weeks. A quantitative analysis was performed to determine the volume fraction of bone ingrowth. At two weeks, there was $12.4 \pm 5.4\%$ bone ingrowth in the stimulated femora compared with $12.7 \pm 6.5\%$ in the controls ($p = 0.74$). At three weeks, bone growth into the stimulated and control implants was $21.1 \pm 6.5\%$ and $22.7 \pm 7.3\%$, respectively ($p = 0.53$). Although a prior study showed that 20 minutes of ultrasound stimulation had a positive effect on bone ingrowth, the results of this study suggest that a treatment of 40 consecutive minutes does not enhance the amount of bone growth into porous metallic implants.

## ABRÉGÉ

Le but de cette étude était d'évaluer la croissance de l'os a l'intérieur d'implants fait de tantalum, suite à la transmission d'ultrasons par pulsations non invasifs. Trois implants cylindiques et trans-cortique ont été inséré dans les deux fémurs de 12 chiens. Une des deux jambe reçut chaque jour pendant 40 minutes consécutives des ultrasons sur l'implant central alors que l'autre jambe servait de contrôle. Six des 12 chiens ont reçu ce traitement pendant deux semaines alors que les six autres ont reçu pour une durée de trois semaines. Nous avons procédé à l'analyse quantitative des données pour nous permettre de déterminer l'augmentation de la croissance de l'os dans l'implant. A deux semaines, le degré d'augmentation de la croissance de l'os a l'intérieur des implants était $12.4 \pm 5.4\%$ dans les implants qui avaient reçu les ultrasons et de $12.7 \pm 6.5\%$ ($p=0.74$) dans les contrôles. A trois semaines, le degré d'augmentation de la croissance de l'os dans les implants qui ont reçu les ultrasons et les contrôles étaient respectivement $21.1 \pm 6.5\%$ et $22.7 \pm 7.3\%$ ($p=.53$). Même si une étude antérieure avait démontré que l'exposition a des ultrasons pendant 20 minutes consécutives avait un effet positif sur la croissance de l'os à l'intérieur des implants, les résultats de la présente étude suggèrent que l'exposition à des ultrasons pendant 40 minutes consécutives n'a pas le même effet positif sur la croissance de l'os a l'intérieur des implants poreux métalliques.

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To Stacey,

forever, with all my love.

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# I. INTRODUCTION

Total joint arthroplasty is a surgical procedure whereby the articulating surfaces of a natural diarthrodial joint are replaced by a combination of artificial implants, usually made of metal and polyethylene. Osteoarthritis, rheumatoid arthritis, avascular necrosis, congenital dislocation, and trauma are common orthopaedic problems that lead to management by total joint arthroplasty. As the elderly population in North America is increasing, arthritis is becoming substantially more prevalent. Of the different types of arthritis, osteoarthritis is by far the most common.

Osteoarthritis is caused by degenerative changes in joints that have usually been affected by developmental deformities, vascular insufficiency, previous disease, or injury. Because the lower extremity joints such as the hip and knee are subject to high in vivo loads, they are more often affected with osteoarthritis than upper extremity joints. The pathology involves slow but progressive degeneration of the articulating cartilage leading to partial or near exposure of the underlying bones. Over time, as cartilage function is lost, the progressive inflammatory changes that occur in the joint result in painful articulation, eventually restricting movement. Patients suffering from this condition can obtain substantial relief by prosthetic joint replacements which substitute the diseased or damaged surfaces of bones with plastic and/or metal, providing smooth articulating surfaces. The goal of a joint replacement is to obtain a painless, durable, and functional joint.

In total hip arthroplasty, for example, the femoral head and the articulating surface of the acetabulum are both removed (Figures 1 and 2). The femoral component is comprised of an intraosseous stem that is inserted down the intramedullary canal of the femur and an extraosseous articulating head made of metal or ceramic. The acetabular component, typically hemispherical, consists of a metal socket with a plastic liner.

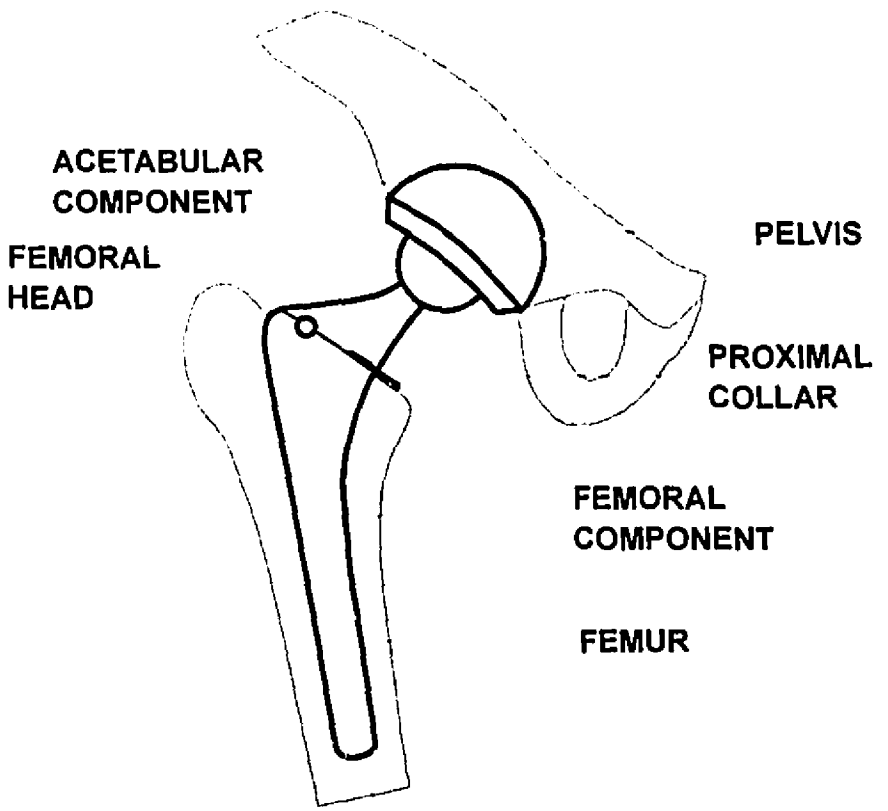



Figure 1. Schematic drawing of a total hip replacement. [replicated with permission of Chan, F.W.: Evaluation of initial mechanical hip implants under physiological loading., Master's Thesis, McGill University, 1995.]

Figure 2. Radiograph of a total hip arthroplasty showing the metallic stem of the implant within the femoral shaft and the acetabular cup implanted in the pelvis.

Preoperatively, the surgeon has many choices in the selection of prosthesis type. Implants are typically fabricated from either titanium or cobalt-chromium alloy. Femoral prostheses are available either with straight or curved stems, and both acetabular and femoral implants can be one piece or modular designs. They can be further categorized into two classes, cemented and cementless, depending on their mode of fixation in the host bone.

Cemented hip implants have been in use since the late 1960's and utilize polymethylmethacrylate (PMMA) as a filler, or grouting agent, between the implant and the host bone. The principal advantage of cement is that it achieves immediate stability between the implant and surrounding bone. Clinically, the durability of cemented femoral components has improved substantially in the last decade. Harris demonstrated in primary total hip arthroplasty with good cementing technique that the revision frequency for aseptic loosening at 15 to 18 years following the initial operation was only 2% to 3%, including patients that were under 50 years of age (1). However, not all reports of cemented hip arthroplasty are as favourable, especially in younger patients, as a result of mechanical deterioration of the implant-cement-bone interfaces (2).

In the 1970's porous coated hip implants were developed as an alternative to those that require cement (Figure 3). These implants have a porous coating on the femoral and acetabular components that provide a surface for bone to grow directly into the implants in order to obtain biological fixation. There are stringent requirements for bone ingrowth.

These include appropriate material, pore size, and initial stability, as discussed in the following chapter.

Figure 3. One type of femoral implant design used for non cemented total hip arthroplasty.

Histological analyses of noncemented hip prostheses have revealed that some implants fail to become bone ingrown, instead becoming encapsulated in fibrous tissue. With bone ingrown prostheses, often only a small fraction of the available porosity becomes ingrown with bone (3-7). Although the minimum amount of bone ingrowth for long term implant stability is not known, it is probable that more abundant ingrowth would lead to a more durable implant.

A procedure that could increase the rate and/or extent of bone ingrowth would increase the reliability and success of noncemented total joint arthroplasty. This would be of particular importance in revision surgery where compromised bone stock acts as a deterrent to bone ingrowth. It has been well demonstrated that bone-implant gaps, which are created because of loosening or during implant removal, decrease the reliability of bone ingrowth (8-10). It has also been shown that femoral hip components that do become bone ingrown produce higher clinical scores (less pain and limp) than those with fibrous tissue ingrowth (11). Increasing the probability and/or extent of bone ingrowth in suboptimal conditions would, therefore, increase the clinical success of noncemented joint prostheses. This thesis investigates the possibility of influencing the extent of porous implant fixation by bone ingrowth via the external application of a low intensity ultrasound stimulus.

# II. LITERATURE REVIEW

Extensive research in the field of biological fixation has taken place over the past few decades. Factors such as optimum pore size, rate of ingrowth, interface strength, suitable materials, initial stability, and the types of implant surfaces have been investigated, in addition to various techniques of enhancing the rate and extent of bone ingrowth.

## A. The Noncemented Prosthesis-History

The self-locking, cobalt based alloy Moore endoprosthesis was the first metallic implant to utilize the concept of biological fixation (12). The implant was made with large fenestrations into which bone grafts were inserted so that fusion between the graft and native bone would take place providing implant fixation within the host bone.

Among the first reports of porous metal fabrication for an implant material was that of Hirschorn and Reynolds in 1968 (13). Using powder metallurgy techniques, they described the production of porous cobalt-chromium alloy with an average pore size of ten to 20 micrometers ($\mu$m). They coated small cylinders with this porosity and surgically implanted them into the muscle of dogs. Twenty-eight days following implantation, it was found that tissue ingrowth into the porous coating had occurred. It was then concluded that this porosity had the ability to provide a means of bonding the implant to the surrounding tissue. Hirschorn and Reynolds postulated that the minimum pore size for

tissue ingrowth is approximately ten microns.

In 1971 Hirschorn et al. described the fabrication of porous coated titanium implants, also using powder metallurgy techniques (14). Titanium was chosen due to its increased availability and its lower modulus of elasticity compared with cobalt-chromium based alloy. It was believed that the titanium would result in a substantial decrease in stress within the prosthesis and at the tissue-implant interface. Implants with a pore size of approximately 200 $\mu$m were inserted into the femora of rabbits and dogs. After 49 days, histological analysis demonstrated bone growth into the porous coating. However, when implants with a pore size of less than 15 $\mu$m were subsequently evaluated, only fibrous tissue was observed to grow into the implants. This study provided a basis for the concept of a minimum pore size that would permit bone ingrowth to occur.

In 1970, Hahn and Palich described the fabrication of titanium implants that were coated with a plasma spray of titanium hydride powder, resulting in pores ranging in size from 50 to 75 $\mu$m (15). Cylindrical implants were placed into the femora of sheep for periods of 14 and 26 weeks. The heads of the implants underwent torque testing which resulted in the heads being sheared from the implants prior to failure of the implant-bone interfaces. Shearing occurred at an average interface shear stress of 13.8 MPa (at 14 weeks) indicating the development of bone ingrowth with very high implant attachment strength.

Subsequently, Galante et al. reported a porous coating produced by moulding and sintering short titanium fibres (16,17). Implants coated with these sintered fibres were implanted into the cancellous bone of rabbit and dog femora. Upon histological examination, deep bony penetration was observed into the implants at three weeks postimplantation.

Simultaneous with the studies using titanium fibre coated implants, several studies were conducted using powder-made porous coated cobalt-chromium implants. In 1971, Welsh et al. designed two implants that differed with respect to pore size (18). A smaller powder yielded a pore size of 20 to 30 $\mu$m, and a larger powder yielded a pore size of 50 to 100 $\mu$m. The implants were inserted into the lateral aspect of canine femora. Mechanical and histological analyses were conducted immediately following surgery and at four months postimplantation. Histologically, both woven and lamellar new bone, with osteoblasts and osteocytes within lacunae, was deposited in direct relation to the implant with the larger pore size only. Uncalcified tissue was found within the porous coating of the implants with the smaller pore size.

In summary, the late 1960's and early 1970's marked the beginning of the era of noncemented, porous coated surgical implants. Bone ingrowth was conclusively proven to be an effective method of implant fixation. At this time, titanium and cobalt-chromium alloys were the predominant metals used in the fabrication of porous coatings for orthopaedic prostheses. Titanium was generally used as a fiber metal mesh, while the

geometry of cobalt-chromium was as sintered powder particles, or beads.

## B. Bone Ingrowth-Cellular Aspects

The cellular aspects of bone growth into metallic implants are often described with reference to fracture healing (7). Therefore, similar to fracture healing, bone ingrowth is a time dependent process that can be described by three time-dependent phases.

The initial phase, the inflammatory phase, lasts approximately one week. It involves a nonspecific response and a haematoma, typically composed of red blood cells, fibrin, and other marrow and cellular elements, permeating the porous surface of the implant. This haematoma is replaced by osteoprogenitor mesenchymal cells which eventually contribute to the formation of either fibrous tissue or bone.

The second phase, or the reparative phase, involves the initiation of bone formation in the porous coating. It usually begins within one or two weeks following implantation, however, it has been shown to occur as early as four days postoperatively in rabbits (7,19-21). In this phase, osteoblasts begin to mature from the osteoprogenitor cells to form osteoid which eventually undergoes calcification to form woven bone. The corticomedullary junction has been shown to be the most active site of calcification. The trabeculae of the woven bone then coalesce within the porous surface of the prosthesis and begin to form a biological and mechanical three-dimensional, interlocking structure.

The final phase is the remodelling phase which involves a transition from intramembranous to appositional ossification. Consequently, mature lamellar bone is formed. This transition typically occurs four to six weeks following surgery, however, it has been noted to occur as early as two weeks postoperatively (7).

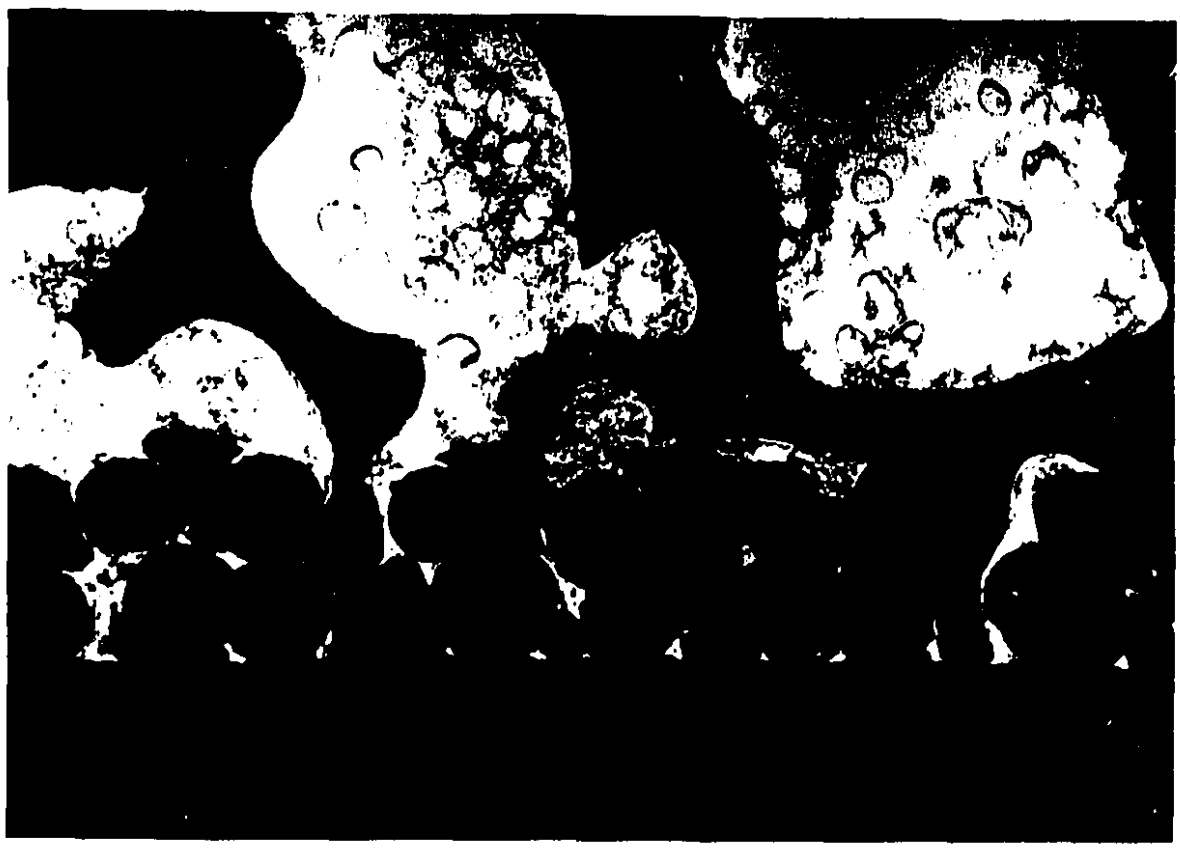


Figure 4. Microscopic view of bone growth into a metallic porous coating. The bone (gray) is grown between the metallic beads (black circles) producing biological fixation.

## C. Factors Affecting Bone Ingrowth

### Motion

Cameron et al. devised a series of experiments in order to study the effects of micromotion and macromotion on bone ingrowth (22). In 1972 they implanted a porous coated cobalt chromium staple into rabbit tibiae. The soleus tendon was attached to the staple in order to create micromotion. Bone grew into the porous coating without any adverse affects.

In a second experiment, one year later, porous coated staples were inserted across an osteotomy site which resulted in macromotion at the staple insertion (23). A dense fibrous tissue was formed, surrounding, but not permeating the staple. It was therefore concluded that bone ingrowth will occur with micromotion but not macromotion. No specific definition of these terms was provided.

Approximately ten years later, Pilliar et al. attempted to define micromotion and macromotion (24). It was concluded that bone ingrowth will occur with motion up to 28 $\mu$m, however, movement of 150 $\mu$m, or more, results in connective tissue fixation only. A recent study by Burke et al. suggested that micromotion should be limited to as little as 40 to 50 $\mu$m to ensure bone ingrowth (25).

## Gaps

Cameron et al. conducted an experiment utilizing cobalt chromium porous coated implants in order to address the issue of maximum gap allowed between bone and the porous surface of an implant for bone ingrowth to occur (8). They evaluated gaps of 0 mm, 0.5 mm, 1.0 mm, and 1.5 mm. The implants remained in the bones for two to 12 weeks. Histological evaluation demonstrated bone ingrowth in all implants except those with the largest gaps of 1.5 mm.

In 1981, Bobyn et al. studied bone ingrowth with non-loaded porous coated intramedullary implants (9). They used implants of different diameters, resulting in gaps up to four millimetres between the implant and endosteal cortex. Histological analysis revealed that little or no bone formation occurred with gaps of more than two millimetres. Bone trabeculae were found to bridge gaps of less than two millimetres, with bone ingrowth increasing as the implant surface approached the endosteal cortex.

The effect of initial bone apposition was also investigated by Sandborn et al. in 1983 (10). Implants were surgically inserted into the intramedullary canal of dogs producing gaps in the range of zero millimetres to two millimetres in width. Analyses were conducted at three, six, and 12 weeks postimplantation. It was concluded that for bone ingrowth to occur, initial apposition of the implant to bone is not necessary. New bone was observed to grow into the implant when gaps of as much as two millimetres were

present. However, the rate of maturity and mineralization was enhanced when the gap measured 0.5 mm or less.

**Pore Size**

In the 1970's significant progress was made in the field of noncemented implants when the importance of porosity was recognized. Pore size and interconnectivity were determined to be critical factors in the success of an implant.

In 1972, Lembert, Galante, and Rostoker studied the effect of pore size on bone ingrowth utilizing sintered titanium fiber metal coated implants (26). The pore size of the implants ranged from 190 to 390 $\mu$m. The implants were inserted into the femoral medullary canals of dogs for a period of six weeks. Mechanical testing revealed no statistically significant difference between pore sizes. Complete bone penetration into the porous coating was observed upon histological analyses for most samples. The implants with smaller pore sizes, however, revealed abundant thin trabeculae, while the larger pore size implants revealed fewer but thicker trabeculae.

Subsequently, a study was conducted by Clemow et al. to determine the effect of pore size on interfacial shear strength and bone ingrowth (27). Implants coated with titanium beads were inserted into the femoral medullary canal of dogs. One implant occupied space adjacent to cancellous bone, and the other cortical bone. The pore size of the implants

ranged between 175 and 325 $\mu$m. They concluded that shear strength and bone ingrowth decreased with increasing pore size in both cancellous and cortical implants.

Bobyn et al. also investigated the effect of pore size on bone ingrowth using sintered porous coated cobalt-chromium implants (28). Variation in particle size resulted in pore sizes of 20 to 50 $\mu$m, 50 to 200 $\mu$m, 200 to 400 $\mu$m, and 400 to 800 $\mu$m. They observed that maximum shear strength occurred with the two intermediate pore sizes at eight weeks postimplantation. Histological evaluation revealed complete bone ingrowth throughout the porous coating also at a period of eight weeks following implantation. The optimal pore size for ingrowth was determined to be 50 to 400 $\mu$m. They also concluded that the process of bone ingrowth is complete at eight weeks postimplantation. Cook et al. later confirmed these findings (29).

In summary, it can be concluded that bone ingrowth is a dynamic process with various influencing factors. First, to ensure adequate ingrowth, motion of the implant must be kept to a minimum. Second, press fit is necessary since a gap of 1.5 mm, or more, between the implant surface and bone, results in little, if any, bone ingrowth. Finally, the optimum pore size of the porous coating on cementless implants is in the approximate range of 50 to 400 $\mu$m. Many commercially available cementless implants such as the Multilock (Zimmer, Inc., Warsaw, IN) and the AML (Depuy Inc., Warsaw, IN) possess pore sizes in this range.

## D. Human and Canine Bone Ingrowth

The fact that bone ingrowth in dogs occurs at a faster rate and to a greater extent than in humans is generally agreed upon (30,31). Bacchus et al. reported a study whereby cancellous bone ingrowth was greater in dogs than in humans using cobalt-chromium implants (32). Magee et al. studied the effect of age on canine bone ingrowth and concluded that there was an effect of age on the strength of fixation of porous coated implants (33). It was found that young dogs achieved a much higher strength of fixation when compared with older dogs six weeks postimplantation.

Studies by Collier and Cook have shown that bone ingrowth is always less than 10% and usually less than 5% at implant retrieval (3-6). In 1991, Cook et al. examined 45 retrieved femoral components (6). Thirty-five of the implants were primary stems and ten were revision implants. Bone ingrowth was observed in 27 of the primary implants and five of the revision implants. The amount of ingrowth was rated as none, minimal, moderate, and extensive. Of the primary implants, eight had no ingrowth, 14 had minimal ingrowth, six had moderate ingrowth, and seven had extensive ingrowth. Among the revision implants, five had no ingrowth, three had minimal ingrowth, and two had moderate ingrowth. They reported that no stem had bone ingrowth into more than 10% of the available porosity and that the mean was only 5%. Bone ingrowth was also found to be in distinct patches and inconsistent from one prosthesis to the next, even within a given type of implant.

Bone ingrowth into total knee replacements has also been shown to be sparse. Collier et al. found only 34% of 144 femoral components and 24% of 209 retrieved tibial components to have any bone ingrowth (3).

By contrast, studies involving implants retrieved at autopsy have shown bone ingrowth to be reliable and abundant. Engh et al. conducted a study in 1993 of nine porous coated acetabular components that were retrieved post mortem (34). The mean implantation time was 50 months. Every component had bone growth into the porous coating and the mean ingrowth was 32%.

In 1994, Pidhorz et al. evaluated the amount of bone growth into 11 porous coated acetabular components retrieved at autopsy (35). The cups had a mean implantation period of 41 months. Analysis was conducted at various locations on the interface. Ten of the cups were observed to be bone ingrown with a mean volume fraction of $12.1 \pm 8.2\%$. The mean extent of bone ingrowth at the interface within the outer surface of the porous coating and the host bone was $29.7 \pm 20.1\%$. More bone was found at that interface than within the porous coating, which had a mean of $20.9 \pm 16.6\%$ bone ingrowth. There was also more tendency for bone to be ingrown near the rim of the cups than elsewhere.

A study by Engh et al., in 1995, investigated bone ingrowth in three proximally and five extensively coated femoral components retrieved from seven cadavers at autopsy (36). All eight specimens were found to have some degree of bone ingrowth. A mean of 35%

of the surfaces were found to have bone ingrowth. In those areas where bone was present, 67% of the available porosity on the extensively coated stems was ingrown, whereas 74% ingrowth was found on the proximally coated stems. In both types of implants, it was determined that the most extensive compact bone ingrowth was at the transition regions between the porous and smooth surfaces. The prostheses evaluated in this study had long-term clinical success and demonstrated significantly more bone ingrowth than previously reported with similar prostheses removed due to malfunction.

In summary, the literature indicates that the presence, or extent of bone ingrowth in cementless prostheses is inconsistent. The studies by Collier and Cook revealed minimal bone ingrowth, whereas the investigations of Engh and Pidhorz have revealed substantial amounts. The minimum amount of bone ingrowth necessary to achieve implant stability is yet to be determined.

## E. Methods of Enhancing Bone Ingrowth

A procedure that increased the rate and extent of bone ingrowth would presumably increase the reliability and success of noncemented total joint arthroplasty. As with fracture healing, a large number of studies have been conducted to investigate the possibility of accelerating the process of bone ingrowth.

New bone that is formed during the processes of fracture healing is equivalent to healthy bone in every respect - clinically, radiographically, histochemically, histologically, angiographically, and metabolically (37). It is also identical to healthy bone in terms of its mineral composition. The aim of fracture treatment and bone ingrowth stimulation is to achieve the original structure, mineralization level, and strength as quickly and effectively as possible.

A review of the literature reveals that, to date, over 40 different approaches have been studied in an attempt to stimulate bone repair in fractures, including operative procedures, chemical and biochemical agents, drug treatments, and physical methods (37). Among the physical, external modalities, electrical and ultrasound stimulation have shown some degree of effectiveness. The list of stimulation techniques for bone ingrowth includes autogenous bone grafts, allografts, demineralized bone matrix, fibrin glue, calcium phosphate granules, collagen, periosteal activation agent, tricalcium phosphate coating, hydroxyapatite coating, transforming growth factor, and electrical stimulation (38-63).

In 1987, Lewis et al. conducted a study to evaluate the effect of grafting materials in a cementless implant model (38). Porous coated cobalt chromium implants were inserted into the femoral metaphyses of mongrel dogs and a bone graft material was packed around the implants. Following sacrifice, the femora were extracted and evaluated using radiography, biomechanical testing, and decalcified and undecalcified histology. The conclusion of the study was that equivalent strength and bone ingrowth was achieved using

autograft, fresh-frozen allograft, and tricalcium phosphate granules. It was concluded that when the prosthesis was in direct contact with the bone or the grafting material, a significant increase in stability was achieved.

An assessment of autograft, freeze-dried allograft, and fibrin glue, as enhancements of fixation of porous coated implants, was conducted by Kienapfel et al. in 1990 (39). The humeri of 27 dogs were implanted with titanium implants. Polyethylene spacers were used on the implants in order to maintain a gap of three millimetres between the porous surface of the implants and the adjacent bone. Each animal had the implants placed bilaterally. One humerus received the enhancement material in the gap, while the other was left empty. It was found that the autograft treated implants had a six fold higher shear strength than the paired controls and the allograft treated implants had twice the shear strength of their paired controls (although not significant, $p=0.12$). No strength difference for the fibrin glue treated implants was observed. Histological evaluation demonstrated that bone ingrowth was consistently present in the autograft treated implants, occasionally in the allograft treated implants, and never in the fibrin glue treated implants. There was a three- to four-fold higher volume fraction of bone ingrowth in the autograft treated implants compared with their paired controls. The conclusion of the study was that at four weeks postimplantation, the autograft treated implants provided higher values for strength of fixation and bone ingrowth than either the allograft treated or the fibrin glue treated implants. It was also concluded that fibrin glue did not have an enhancing effect on bone ingrowth or strength of fixation.

Rivero et al. conducted a study in 1988 whereby porous titanium fiber implants treated with calcium phosphate coating were inserted into the humeri and olecranons of dogs for periods of one, two, four, and six weeks (40). Biomechanical and histological evaluations were conducted following sacrifice. At four weeks, the mean shear strength of biological fixation was 24% greater for the implants that were coated with the calcium phosphate than the paired controls. No difference was observed at the other time periods. Histologically, it was found that bone formed in direct contact with the coating on the metal fibres of the implants, demonstrating its osteoconductive behaviour. However, there was no significant difference in bone ingrowth volume at any time period between the treated implants and the controls.

Collier et al. conducted a study in 1988 on the effect of plasma sprayed tricalcium phosphate (TCP) and hydroxyapatite (HA) coatings on orthopaedic implants (41). The purpose of the study was to investigate whether a change from alpha-TCP to HA occurs in vitro and in vivo and what effect this transformation has on the strength of the bond between the implant and the material. Hydroxyapatite or TCP was plasma sprayed onto glass slides which were placed into test tubes containing either saline or blood plasma. The samples were left in the solutions for six days. After being air-dried for 24 hours, x-ray diffraction patterns were made and compared to those obtained from HA and TCP coated slides not subjected to the solutions. Diffraction patterns were also obtained from TCP and HA coated rods that were implanted into rabbit tibiae for a period of 12 weeks. The results demonstrated that TCP coatings transformed into HA in as little as six days

of submersion in saline and serum. Pull-out tests were conducted on the rods and revealed that the TCP coated implants underwent failure at the interface which was associated with a reduction in shear strength of nearly 75%. Much of the TCP had been transformed to HA as determined by x-ray diffraction. The conclusion of this study was that the strength of the bond between metal or glass, and either TCP or HA, degrades in an aqueous environment, raising concern about their long term efficacy as implant fixation systems.

In 1980, Salman and Park conducted a study whereby cylindrical implants fabricated from Co-Cr-Mo alloy, with an average pore size of 190 $\mu$m, were inserted into the femora of dogs (42). Electrical stimulation of 1.35 V was directly attached to the implants. The results demonstrated that tensile strength substantially increased in the stimulated femora at periods of up to 12 weeks. It was postulated that the increase in strength was a result of an increase in bone ingrowth in the stimulated femora.

Rivero et al. conducted a study in 1986 on the effect of pulsing electromagnetic fields (PEMF) on bone growth into a porous material (43). Porous titanium composite implants were bilaterally inserted into the tibiae of eight mongrel dogs. Two days following surgery stimulation of one side of each animal began for ten hours per day, and continued for 26 days. The contralateral side of each dog served as the control. PEMF was delivered by external metallic coils and had a frequency of two Hz and an amplitude of 1.6 mV. Each animal was sacrificed four weeks postoperatively, at which time the tibiae were retrieved. Each specimen underwent mechanical pull-out testing and histological analysis

for the quantification of bone ingrowth volume fraction. The results demonstrated no significant difference in shear strength for those treated with PEMF as compared to the controls. Histologically, bone ingrowth was observed in all retrieved specimens, however, no significant difference was observed between the treated and control implants.

In 1987, a study was conducted by Shimizu et al. in order to evaluate the effect of PEMF on bone growth into porous calcium ceramics (44). Ceramic, cylindrical implants, fabricated from HA, were inserted into the tibial medullary canal of adult rabbits. The implants were fabricated with totally interconnected pores. Postoperatively, the animals were divided into two groups. One group received daily treatment of PEMF for eight hours and the second group served as the control. The magnetic field was produced by a transducer that provided a pulse burst of 1.8 gauss at a frequency of 1.5 Hz. The animals were sacrificed at one, two, three, four, and six weeks postoperatively. Using scanning electron microscopy and computer digital analysis, histological evaluation was conducted. At two weeks postimplantation the implants treated with PEMF demonstrated $11.5 \pm 3.0\%$ ingrowth as compared to the controls which had $5.1 \pm 1.4\%$ ($p < 0.05$). At six weeks postimplantation the stimulated HA implants had $35.8 \pm 3.2\%$ ingrowth compared to the controls which had $41.8 \pm 2.6\%$ (but not significant). It was postulated that the decrease in the effect of PEMF at the later time period was most likely due to bone remodelling.

The effect of prostaglandin F2 alpha on bone growth into porous coated implants was investigated in 1990 by Trancik and Vinson (45). The foundation for the study was that medications that inhibit prostaglandin synthetase have demonstrated the ability to impair fracture healing and inhibit bone ingrowth. For the study, porous coated cobalt chromium implants were inserted into the distal femoral metaphyses of rabbits. Fifteen rabbits were administered normal saline injections and 15 were administered prostaglandin F2 alpha (250 mcg/kg/day). The rabbits were sacrificed at time periods of two, four, and eight weeks postimplantation. The specimens were evaluated by undecalcified ground section histology and histomorphometry in order to determine the degree of bone ingrowth. The study revealed an increase of bone ingrowth in the PGF2-alpha treated groups at two and four weeks postimplantation as compared to the control groups.

Of all these methods of bone growth stimulation, autogenous bone grafting has been the most effective for defect filling and bone incorporation (38-39). The calcium phosphate coating has been most successful at causing osteoconduction and a slight increase in bony apposition and ingrowth within the first few weeks following surgery (40). PGF2-alpha has also shown to have an enhancing of bone ingrowth (45). Experimental and clinical investigations of electrical stimulation and PEMF, as bone growth stimulants, have provided variable results (42-44). The remaining methods have shown either no effect or no conclusive evidence of accelerating or enhancing the extent of bone ingrowth.

Another modality that is under investigation as an accelerator and enhancer of bone growth into porous coated implants is non-invasive low intensity pulsed ultrasound (NILIUS) (63). The work of Tanzer et al. was based on the findings of several studies demonstrating that NILIUS is capable of accelerating fracture healing both experimentally and clinically (37,64-68). A description of ultrasound technology and experimental data follows. Additional details are found in Appendix I.

1. Ultrasound- Definition

Ultrasound is a term that is applied to sound frequencies that are beyond the range of human hearing, that is 20 kHz or higher. There are commonly two types of transducers used in practice, the magnetostrictive and the piezoelectric (37). The wavelengths of ultrasound are very short, allowing easy emission of waves in the form of directional, collimated beams. This characteristic also allows ultrasound to exert tissue effects at the cellular and molecular levels (37).

There are currently three different types of ultrasound that are recognized based on intensity and frequency. The intensity is expressed in $W/cm^2$ and represents the energy transferred by an ultrasound wave over a given area. The frequency is a function of cycles that the wave makes between its most positive and negative amplitude values per second. The first type of ultrasound, high frequency ultrasound, is used in physical therapy. It has a frequency range of 800-1500 kHz and intensities between 0.05 and 3.0 $W/cm^2$. Low

frequency ultrasound is used in stomatology for dental calculus removal, cleaning of precision parts, treatment of ulcers, circulatory problems, local infections, as well as the stimulation of fracture healing. It has a frequency of approximately 40 kHz and intensities between 40 and 80 $W/cm^2$. Finally, high intensity ultrasound is used in operative medicine for the division and uniting of tissues. Its frequency range is between 20 and 40 kHz and its intensities are between 100 and 200 $W/cm^2$.

Therapeutic ultrasound has been in use in physical therapy for several decades. A survey was conducted in 1992 by Lambrechtsen et al. on the use of ultrasound by physiotherapists (69). The survey included treatment of osteoarthritis, rheumatoid arthritis, cervical slipped disc, lumbar slipped disc, generalized lumbar/back pain, generalized bursitis, generalized tendinitis, and sprains. Nine different forms of therapy were examined including hot packs, infrared light, ice packs, short wave microwaves, diadynamic currents, laser, transcutaneous electric nerve stimulation, and ultrasound. In 1979, a study revealed that ultrasound accounted for only 24% of the treatments, whereas in 1992, Lembrechtsen et al. found that its use doubled to 48%.

## 2. Ultrasound- Characteristics and Mechanism

The mechanism of action of ultrasound is quite complex. The effects are both local and general, immediate and delayed, and extremely variable, owing to the great difficulty in determining a dose-response relationship. It is presumed that a number of effects

contribute to the mechanism, one of which is ultrasound intensity. Experimental and clinical studies have revealed that therapeutic ultrasound varies significantly depending on the sound intensity, the exposure time in minutes, the sound frequency, the radiating area of the transducer, the application technique, the transmission mode, tissue characteristics, reflections at interfaces, the formation of standing waves, and temperature (37,68).

In 1963, Wiedau and Röher made a distinction between the primary and secondary effects of ultrasound (70). They determined that the primary effects are the immediate physical and chemical changes in the sound field, as opposed to the secondary effects which are the general responses of the organism, based on its vascular and neuroanatomic mechanisms.

Sound waves (and ultrasound), unlike light and electromagnetic waves, propagate in the form of longitudinal vibrations. As the wave propagates, each particle in the medium vibrates about the center of its resting position, resulting in a transfer of energy through the medium. This is accomplished by the alternating of pressure states. Experiments by Knoch and Klug have proven that the fracture site does not always have to be stimulated directly (37). The ultrasound can be applied at a distance, however, a greater intensity is required.

The pressure gradient created between the moving particles of matter can be directly measured. It is found to be dependent on particle acceleration and tissue density. With each vibration, the pressure value alternates between a positive value, known as condensation, and a negative value, referred to as rarefaction. This process of alternating positive and negative values is termed "internal tissue massage".

During transmission of an ultrasound wave, energy is transferred due to the attenuation of the intensity as it travels. Some of this energy is absorbed and converted to heat. One speculation as to the mechanism of ultrasound treatment on fracture healing is that the heat that is created results in increased cell metabolism. It should be noted that while ultrasound is being used as a means of heating, nonthermal changes may be occurring simultaneously. The amount of energy absorbed depends on the frequency of the ultrasound wave and the conducting medium. The heat causes the local temperature of the tissues to rise at a rate of 0.7 °C/min. However, as time passes this rate decreases. After a long period of time the temperature approaches, but never exceeds a limiting "final temperature" (37). The composition of the tissues in the path of the beam results in a variation of absorption. Tissues with a high protein content absorb ultrasound more readily than those with higher fat content. Therefore, highly collagenous tissues, such as bone, are heated more than the skin and adipose tissue covering them.

The main advantage of using ultrasound as a source of heat, rather than a nonacoustic method, is that ultrasound allows collagen-rich tissues to be heated preferentially without

producing damage to the skin or subcutaneous adipose lying beneath. The periosteum and superficial cortical bones are among the tissues which can be preferentially heated (68).

While the above information provides evidence that heat is one possible mechanism of action for ultrasound therapy, there are numerous situations where heat plays little or no role. Therapeutic effects of ultrasound, of nonthermal origin, as described below, appear to be significant in tissue regeneration, soft tissue repair, inducing repair of ununited bone fractures, and relieving prosthetic pain. The nonthermal effects are attainable using lower intensities than those needed to ensure physiological heating (68).

The physical mechanism commonly involved in nonthermally induced ultrasound therapy includes cavitation, or bubble formation, which causes acoustic streaming. Acoustic streaming is defined as the unidirectional movement of fluid in an ultrasonic pressure field. Connective tissue fibres and plasma membranes form boundaries within the field producing high velocity gradients. Effects similar to this occur at the surface of any gas bubble in the field. In the case where a boundary is the surface of a cell, characteristics of the cell's behaviour, such as its permeability, may be altered and in turn produce therapeutic effects. When acoustic streaming is sufficiently small it is referred to as microstreaming (68).

There have also been observations of change in membrane permeabilities, active transport processes, and metabolic rates. Melting, and other phase changes may occur,

as well, altering the function and integrity of cellular and subcellular structures (68).

In 1989, Dinno et al. demonstrated that the cellular changes that occur as a result of ultrasound stimulation are not a result of thermal changes (71). It was determined that the alterations in motility and the stimulation and synthesis of cell secretions are associated with a change in the permeability of the plasma membrane and in the transport of ions and molecules across it.

Most recently, Yang et al. demonstrated the effect of low intensity pulsed ultrasound on the healing of soft tissue and bone (72). Biomechanical, biochemical and gene expression analyses were conducted in order to determine the possible mechanism of action of ultrasound. In their study, bilateral closed femoral fractures were produced in rats. The rats were then divided into three groups. All groups received daily ultrasound stimulation of one femur for 15 minutes, ten times within the first 14 days postoperatively. A zirconate titanate transducer with 0.5 MHz frequency, a 15 mm diameter, an intensity of 30 $mW/cm^2$, and a 200 $\mu$sec burst sine wave was used. The study showed that the ultrasound treatment resulted in a larger, stiffer, and stronger callus than the control. There were no significant differences in DNA or collagen contents, however, the larger callus on the treated femora suggested an effect on noncollagenous protein synthesis, or expression of collagen isotypes. Analysis of gene expression supported an effect of ultrasound on cartilage formation and the expression of noncollagenous genes within the callus.

Duarte conducted a study in 1983 whereby rabbits received bilateral fibular osteotomies (67). One leg was treated with low intensity ultrasound for 15 minutes per day. The intensity was low enough to hold the temperature constant (within 0.01°C). This study, which resulted in accelerated fracture healing in the stimulated fibula, confirmed that the appearance of electrical potentials is of non-thermal origin, such as that caused by the piezoelectric effect of ultrasound.

In 1973, Pospisilova illustrated the effects of ultrasound stimulation on connective tissue metabolism (73). He found an acceleration in the formation of specific cells, an influence on polysaccharide metabolism, homeostatic action to balance collagen synthesis, and an effect on collagen lysis.

Aside from the mechanical and electrical effects of ultrasound, it is also postulated that there are physiochemical, chemical, and biological mechanisms that occur in insonated tissues. The biological response is a result of neurohormonal interactions, particularly with respect to activity at the neural end plates (37). These effects play a crucial role in the mechanism of therapeutic ultrasound. A change in any of the physical parameters, for example, the frequency, intensity, or exposure time, will lead to changes in the mechanical, thermal, and chemical effects, which in turn result in an altered biological response.

3. Ultrasound- Fracture Healing Applications

Knoch and Klug conducted a study whereby radial fractures in humans were treated with ultrasound beginning on the sixth day following fracture reduction (37). The radiating area of the ultrasound was measured to be 6.4 $cm^2$, the intensity was 0.5 $W/cm^2$, the treatment time was five minutes, and the number of treatments was ten (applied daily except for on weekends). They concluded that fractures treated with ultrasound were consolidated much earlier than those that did not receive stimulation. Alkaline phosphatase levels were measured and found to be significantly higher on ultrasound treated patients, as was total mineral content.

Subsequently, Knoch and Klug studied the effects of ultrasound on rabbits in which one tibia was osteotomized and immobilized by internal fixation (37). Ultrasound treatment began one week postoperatively, allowing sufficient time for fracture haematoma organization and the fibrous phase of the healing process. A second group of rabbits underwent the same surgical procedure but did not receive stimulation. The experimental group was treated for two minutes, on alternate days, up to a total of four treatments. In the second week postoperatively, the animals were examined radiographically and clinically. At the end of the third week, the animals were sacrificed and prepared for histological examination. At this time the control fractures lacked the radiographic and clinical stability of the stimulated fractures.

A study was also conducted by Knoch and Klug whereby fractures were produced in the tibiae of mature rabbits that were then stimulated with ultrasound (37). They conducted an evaluation of radiographic data, strengtn tests, histology using scanning electron microscopy, bone scintigraphy, angiography, biochemistry, total mineral content, sequential polychrome labelling, and temperature. They found greater and more rapid callus formation in animals treated with ultrasound than in the controls. Upon histological evaluation it was found that callus tissue of the insonated group was more mature than in the nonstimulated group. Lamellar bone formation occurred five weeks earlier in the stimulated group than in the control group. Mechanical testing showed that by day 70, animals treated with ultrasound had attained fracture load and bending strengths equivalent to healthy unfractured tibia. It took 126 days for the control animals to reach this strength. In general, Knoch and Klug concluded that the process of healing occurred to a greater extent and at a quicker rate for animals that were treated with ultrasound as compared to those that were not stimulated.

Duarte demonstrated that NILIUS was effective at stimulating fracture healing of osteotomized fibulae and femoral cortical defects of rabbits within 18 days of treatment (67). Twenty-three rabbits underwent bilateral fibular osteotomies and 22 received bilateral drill holes in their femoral cortices. The wounds were treated with ultrasound for 15 minutes per day. The ultrasound was pulsed and in the form of short bursts, at low intensities (below threshold for cavitation) so that the temperature variation at the injured sites was less than $0.01^{0}C$.

Pilla et al. recently demonstrated that NILIUS is capable of accelerating bone healing of osteotomized fibulae in mature female New Zealand white rabbits by a factor of approximately 1.7 (64). For their study, an ultrasound signal of 200 $\mu$sec bursts of 1.5 MHz sign waves, repeating at 1 kHz, and delivering a $30\pm5$ mW/cm$^2$ incident intensity was used. The fibulae received daily treatments of 20 minutes. There was a statistically significant increase in fibula strength noted on day 14.

Subsequent to the study conducted by Pilla, Heckman undertook a prospective, randomized, placebo controlled, double-blind study on the effectiveness of NILIUS upon the rate of fracture healing (65). Twenty-eight human adults with acute closed or grade 1 open tibial shaft fractures were enroled in this study. Thirteen of the patients underwent 20 minutes of ultrasound stimulation daily, while the remaining 15 patients served as controls. The patients that received ultrasound stimulation had a statistically significant increase in both endosteal and cortical healing of their fractures. No complications or adverse affects were noted as a result of the ultrasound stimulation.

Most recently, Heckman et al. conducted a study of 67 closed or grade 1 open tibial shaft fractures (66). Thirty-three fractures were treated with ultrasound and 34 with a placebo apparatus. At the end of the treatment they found that there was a significant decrease in healing time ($96\pm4.9$ days vs. $154\pm13.7$ days, $p=0.0001$).

4. Ultrasound- Bone Ingrowth Application

Only recently has NILIUS been evaluated for the enhancement of bone growth into metallic porous surfaces. Tanzer et al. have conducted the only study in this field (63). In their study, 22 pairs of fully porous transcortical titanium implants were implanted bilaterally into the femora of 12 dogs. In each dog one femur served as the control while the other underwent daily ultrasound stimulation for a period of 20 minutes. Three dogs were treated for periods of two, three, and four weeks each. Overall, the ultrasound stimulated implants demonstrated an 18% increase in bone ingrowth as compared to the contralateral femur. The ultrasound stimulation was found to have its greatest effect in the first two to three weeks of treatment. At two and three weeks, implants in the stimulated femora demonstrated 21% and 16% greater ingrowth, respectively, than implants in the control femora.

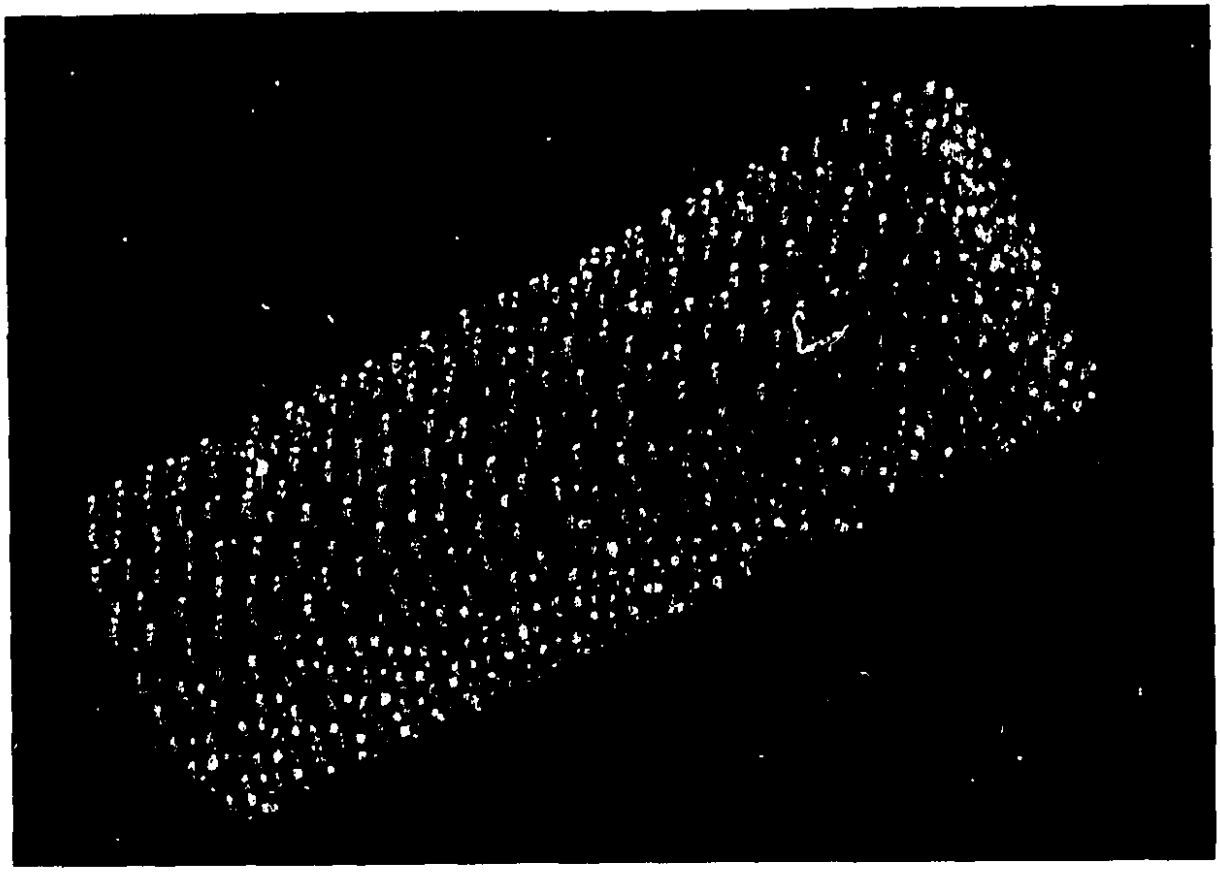


Figure 5. Porous titanium implants used in the study by Tanzer et al. (Duplicated with permission of Tanzer et al.).

In summary, it is evident that non-invasive low intensity pulsed ultrasound has an effect on bone healing. There is much speculation as to its mechanism of action. However, there does seem to be more evidence that the mechanism is of nonthermal origin and that a change in the cell membrane's permeability is of great significance to the mechanism of action.

# III. PURPOSE

Effective enhancement of the rate and extent of bone growth into porous coated prostheses would improve their reliability and clinical function. Based on review of the literature, ultrasound stimulation could potentially represent a very convenient, cost effective, and simple modality for enhancing bone growth into porous coated joint replacement prostheses. An ultrasound transducer is easily portable and relatively inexpensive. Application simply consists of applying ultrasound gel to the skin and leaving the transducer in place for the required treatment period. Patients could initiate treatment immediately following surgery and could conveniently continue treatment in their own homes.

There is sufficient preliminary evidence, from the study by Tanzer et al., of a positive effect of ultrasound stimulation on bone ingrowth to warrant additional investigations (63). Given the potential of NILIUS in the field of noncemented total joint replacement, the **purpose** of this study was to further evaluate its effect on the rate and extent of bone growth into porous tantalum implants.

# III. MATERIALS AND METHODS

## MATERIALS

### A. IMPLANTS

#### 1. Introduction to Porous Tantalum

The two metals most commonly used in the fabrication of cementless implants are titanium based alloy (Ti-6Al-4V) and cobalt-chromium (Co-Cr-Mo) alloy. As well, a variety of porous surfaces have been used for bone ingrowth fixation of total joint replacements. These include sintered cobalt-chromium beads, diffusion bonded titanium fibre metal, and titanium plasma spray surfaces.

The previous study conducted by Tanzer et al. on the effect of NILIUS on bone ingrowth utilized cylinders of commercially pure titanium beads in a transcortical model (63). In the present study, the same transcortical model was used, however, the implants were fabricated from a new porous tantalum material.

Porous tantalum consists of regular, interconnecting, sphere-like pores, formed by a lattice work of continuous struts, arranged in a regular three-dimensional pattern (Figure 6). The porous tantalum material is fabricated by the deposition of commercially pure tantalum onto a vitreous carbon skeleton possessing an interconnecting dodecahedron array

of pores. The skeleton is produced by the pyrolysis of a thermosetting polyurethane foam substrate. Chemical vapour infiltration (CVI) technology is used for the deposition of tantalum onto the carbon skeleton. The tantalum is deposited with a depth of ten to 100 $\mu$m. A detailed description of the CVI process is found in Appendix B.

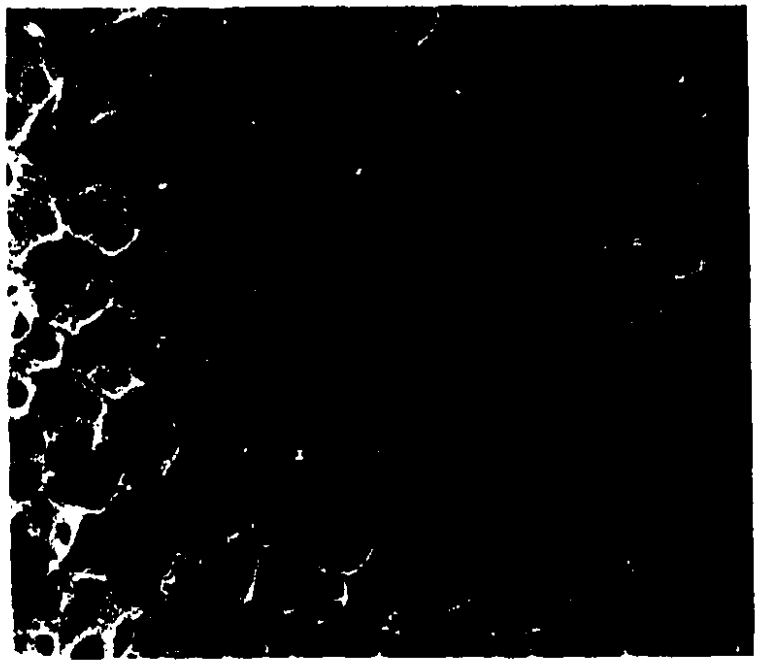


Figure 6. Scanning electron microscopic view of the porous tantalum implant material (150x).

## 2. Tantalum as a Biocompatible Material

The term "biocompatibility" is used to describe the biological response associated with the use of a natural or manmade material in a biological system (74). As a biocompatible material, tantalum is chemically stable and is only attacked by strong acids and alkalis (75-77). The combination of excellent mechanical properties and resistance to chemical attack lead to the consideration of tantalum as a material for use in human implants.

The physical properties of pure, commercially available tantalum are given in Table 1 (78):

**Physical Properties of Tantalum**

| | |
|---|---|
| Elastic Modulus: | 185 GPa |
| Yield of Strength: | 165 MPa |
| Elongation to Failure: | 40% |
| Tensile Strength: | 205 MPa |
| Density: | 16.9 g/cm$^3$ |
| Melting Point: | 3000 °C |
| Hardness (Hv): | 110 |

Tantalum was first implanted in 1940 by Burke who reported that the material had high resistance to various strong acids (75). In 1987, Zitter and Plenk reported lower corrosion current density and higher corrosion resistance for tantalum than for titanium and Ti6Al4V under similar study conditions (76).

There have been very few reports indicating tantalum degradation in vivo. Johnson et al. conducted a study whereby they concluded that when passivated tantalum is deliberately used as an anode electrode, tissue discoloration does not occur (77). However, when there is slight motion between the implant and the tissue, slight discoloration is occasionally observed, as revealed by von Holst et al. and Pfluger et al. (79,80). They hypothesized that the discoloration was probably secondary to oxide particulate removal.

Comparative studies have shown that tantalum does not inhibit bone growth or cause bone resorption, as gold and cobalt based alloys do. Rather, it becomes tightly enveloped by new osseous tissue shortly after implantation (81,82). Osseous ingrowth has been demonstrated up to and within tantalum implants. It has been shown to result in complete, strong, long term osseointegration in both dental and orthopaedic applications under unloaded and heavily loaded conditions for periods as long as eight to 12 years (83-85).

A preliminary study with porous tantalum implants, of the type used in the present study, has shown that the material is suitable for bone ingrowth. In 1995, Stackpool et al. inserted transcortical porous tantalum implants bilaterally into the femora of 12 dogs (86). Scanning electron microscopy and computer image analysis were conducted to evaluate the volume fraction of bone growth into the implants at periods of four, 16 and 52 weeks postimplantation. The extent of bone ingrowth was approximately 49% in the four week implants and 71% in both the 16 week and 52 week implants (Figure 7).

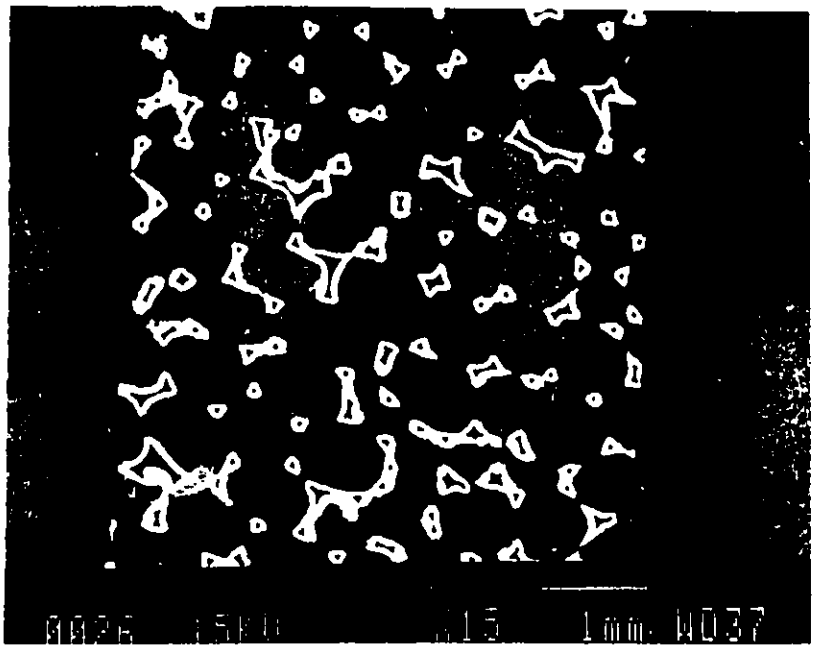


Figure 7. Scanning electron micrograph demonstrating 70% bone ingrowth (reproduced with permission of Stackpool et al., 1995).

Given its properties and potential advantages, porous tantalum was selected as the implant material for the purposes of this study. This provided the opportunity to characterize the tissue response to a new orthopaedic biomaterial with and without ultrasound stimulation.

## 3. Rationale for Using Porous Tantalum

Porous tantalum is an interesting candidate material for a variety of orthopaedic uses. As described earlier, tantalum is a very biocompatible material with a long history of implant applications. The porous tantalum used in this study possesses a high strength to porosity ratio and hence could be used for structural as well as nonstructural (space-filling) functions. It can be manufactured as a bulk material or as an implant coating for joint replacement prostheses. It is easily machinable and can be conveniently fabricated in a variety of implant shapes and configurations. In addition, the material is highly porous (80% porosity), more so than conventional porous coatings (30%-35% for sintered beads and 35%-40% for fibre metal [28]), and thus can allow a large amount of bone ingrowth and the development of a strong implant-bone interface.

If used as a coating, porous tantalum can be applied to the substrate with much lower heat than conventional porous coatings. During fabrication of conventional porous coatings, for example sintered beads, the heat that is created has a deleterious effect on machining tolerances, implant substrate metallurgy, and the fatigue strength of the implant (87-90). CVI, on the other hand, preserves the properties of the implant, including its strength.

4. Porous Tantalum Implant

The tantalum implants used in this study measured nine millimetres in length by five millimetres in diameter (Figure 8). The porous network consisted of regular, interconnecting, sphere-like pores formed by a lattice of continuous struts organized in a regular three-dimensional dodecahedron array (Figure 5). The manufacturer (Implex, Corp., Allendale, NJ) has determined the volume porosity to be approximately 80% and the mean pore size to be about 700 $\mu$m.

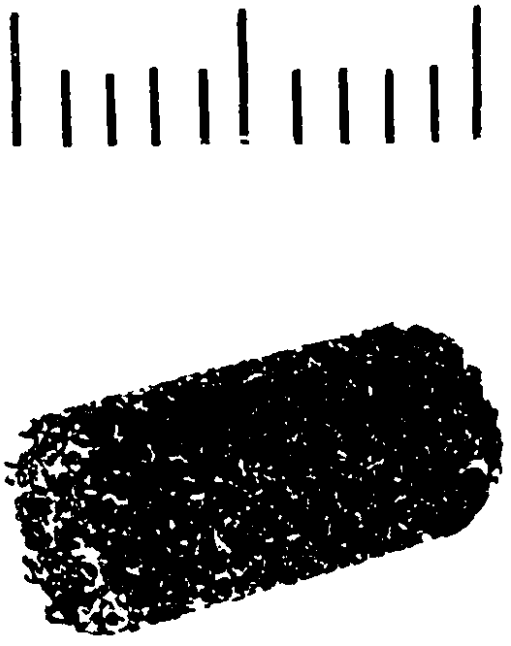


Figure 8. The transcortical tantalum implant. Note the bevelled edge for ease of insertion into the cortical bone drill hole.

## B. Ultrasound Transducer

The ultrasound signal used in this study was produced by a 2.5 cm zirconate-titanate (ceramic lead composite) transducer supplied by Exogen Inc. (West Caldwell, NJ) (Figure 9). Exogen has obtained Food and Drug Administration approval and is currently marketing the transducers for the stimulation of fracture healing. The zirconate-titanate transducer was cut in the shape of a disk. The ultrasound was pulsed at 200 microsecond bursts of 1.5 megahertz sine waves, repeating at a 1 kHz frequency. The average intensity of the beam was 30 $mW/cm^2$. The parameters of the signal were identical to those in the studies conducted by Pilla et al. (64), Heckman et al. (65,66), and Tanzer et al. (63). By beam profiling, Exogen determined that the ultrasound had an affect over an area of 5.4 $cm^2$ and a depth of approximately 12 cm.

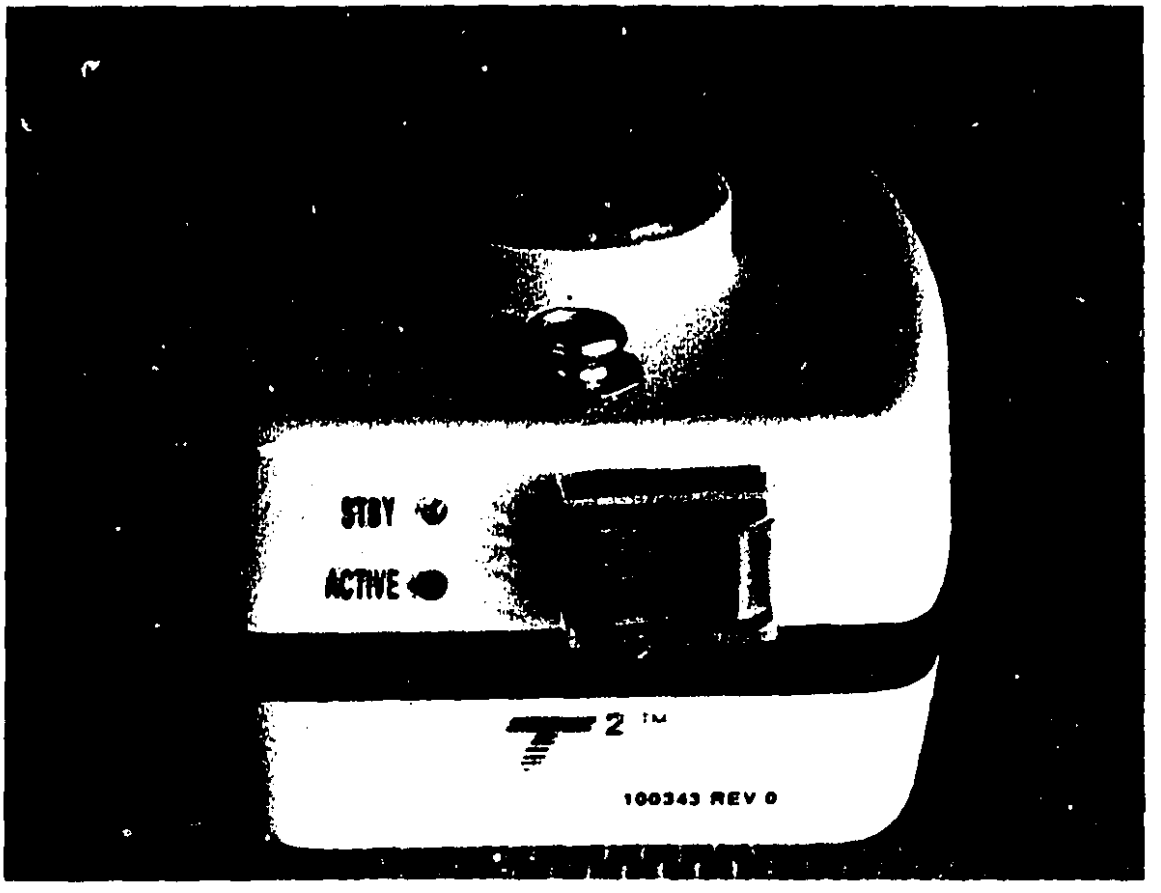



Figure 9. The ultrasound transducer.

# METHODS

## A. Implant Model

In order to meet the objectives of this study, a transcortical implant model was chosen. The transcortical model allows for control over the reproducibility of the implant fit, immediate stability of the implant, reproducibility of implant loading, stress shielding, implant retrievability, and histological evaluation. It has been used in several previous studies and has proven to be extremely useful for examining tissue response to implants in bone. The model is uncomplicated and offers many advantages over other implant models:

1) With reliable instrumentation, holes can be drilled with accuracy and in perpendicular alignment with the long axis of the femur.

2) The bone type forming the interface with the implant is consistent and thus allows equitable comparison of histological data.

3) Cortical bone is appropriate to study since retrieval analyses have shown that the most consistent and abundant source of bone ingrowth in femoral hip prostheses is from the cortical region (9,91).

4) It also allows for data comparison with previous studies which have used a similar model.

These characteristics of the transcortical model for studying bone ingrowth make it reliable as a preliminary study and a foundation for future studies.

## B. Overview of the Study Protocol

Three transcortical implants were surgically inserted bilaterally into the femoral diaphysis of each experimental dog. One femur served as the control side while the contralateral femur underwent daily 40 consecutive minutes of ultrasound stimulation. Stimulation began on the first day postoperatively. Six dogs underwent treatment for two weeks and six dogs underwent treatment for three weeks. The harvested femora were processed for undecalcified thin section histology to enable quantification of bone ingrowth by scanning electron microscopy.

## C. Details of the Study Protocol

### Animal Selection

Mature, mongrel dogs, of both sexes, ranging in weight from 25 kg to 30 kg were used for all studies. All the dogs evaluated in the study were skeletally mature as verified

radiographically by the presence of a closed growth plate prior to surgery.

**Anaesthesia**

Prior to surgery, the animals were anaesthetized with Sodium Pentobarbitol (Somnotol- 65 mg/ml, MTC Pharmaceuticals, Cambridge, Ont. ). The dose was 33 mg/kg injected intravenously into the cephalic vein. The animals were then intubated, placed on a respirator (Penlon, Nuffield Anaesthesia Ventilator Series 200, Abingdon, Oxon, UK), and remained anaesthetized using Halothane (0.5-1.5%, MTC Pharmaceuticals, Cambridge, Ont.).

**Preparation for Surgery**

The hind legs of the dogs were completely shaved prior to surgery. They were then prepared with an antiseptic solution of 1% providone-iodine (Proviodine, Rougier, Inc., Chambly, Que.) and draped using standard aseptic surgical technique. After completion of the first surgery the animals were turned over, re-prepared, re-draped, and the surgeons were re-gloved.

## Surgical Technique

An incision was made from approximately 20 mm below the greater trochanter to within 20 mm of the lateral condyle of the knee in preparation for a lateral approach to the femoral diaphysis. The underlying fascia lata was incised exposing the underlying muscle. The vasus lateralis was retracted anteriorly and the femur was exposed. Care was taken to minimize removal of the periosteum while accessing the surface of the femur.

Specialized instrumentation was designed to ensure aligned fit of the implants and accurate reproducibility (Figure 10). The instruments included an adjustable femoral jig that provided a stable base for reproducible implant introduction into the femora and a drill guide, or bushing, that ensured that the drill holes were made perpendicular to the long axis of the femur.

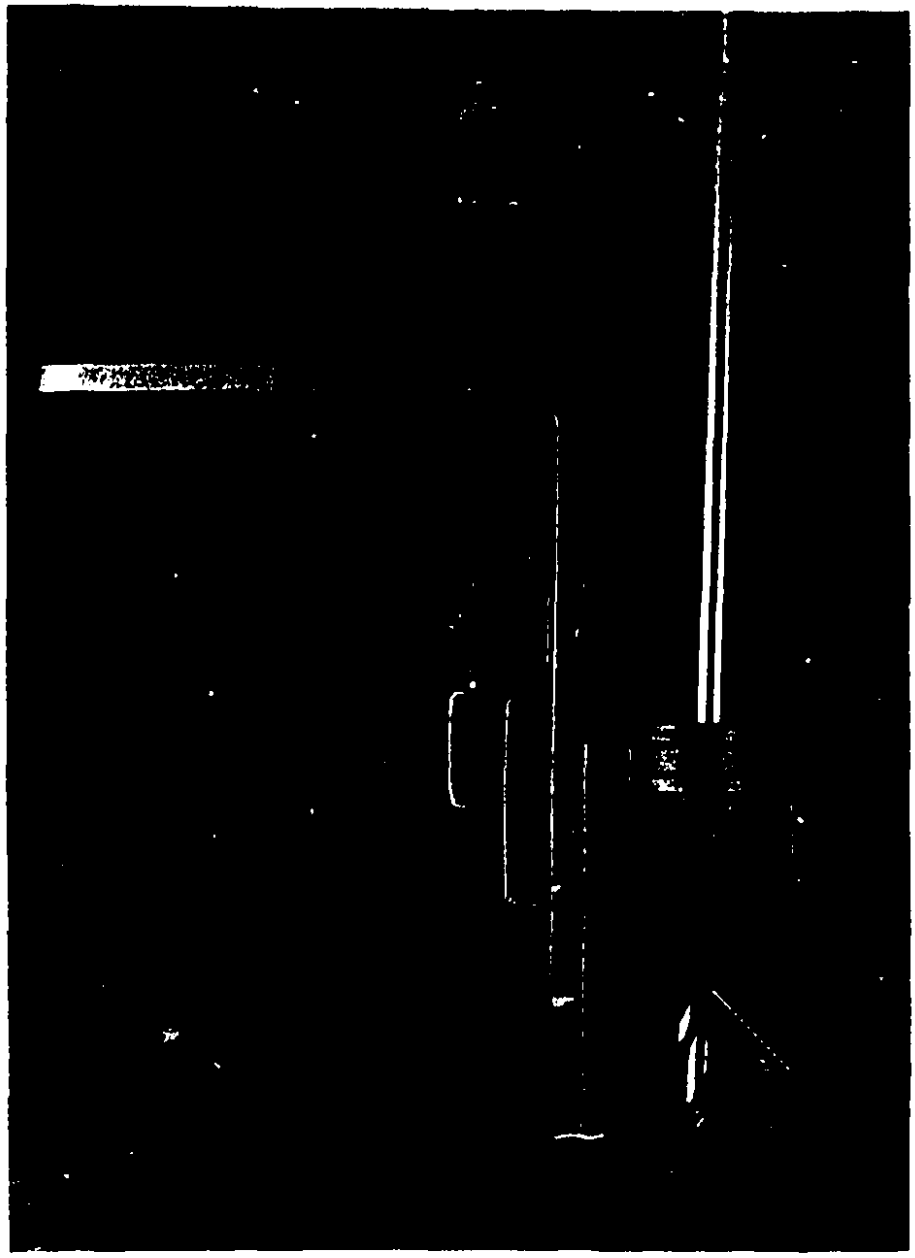


Figure 10. Femoral clamp and drill guide.

Drill sites were chosen approximately 15 mm apart and were designated as 1P, 2P, and 3P, corresponding to proximal, middle, and distal, respectively. Placement of the implants 15 mm apart was necessary to avoid stress concentrations that could induce a fracture. It also provided the opportunity to assess the effect of ultrasound over a distance. Since the radiating area of the transducer's signal was 5.4 $cm^2$, the amount of bone growth into the central target implants could be compared with that of the implants a distance of 15 mm away (Figure 11). A radiating area of 5.4 $cm^2$ has a diameter of 26 mm and a radius of 13 mm. Therefore, the implants that were placed 15 mm away from the central implant were not directly in the ultrasound field but may have been affected by the tendency for ultrasound energy to be propagated within bone.

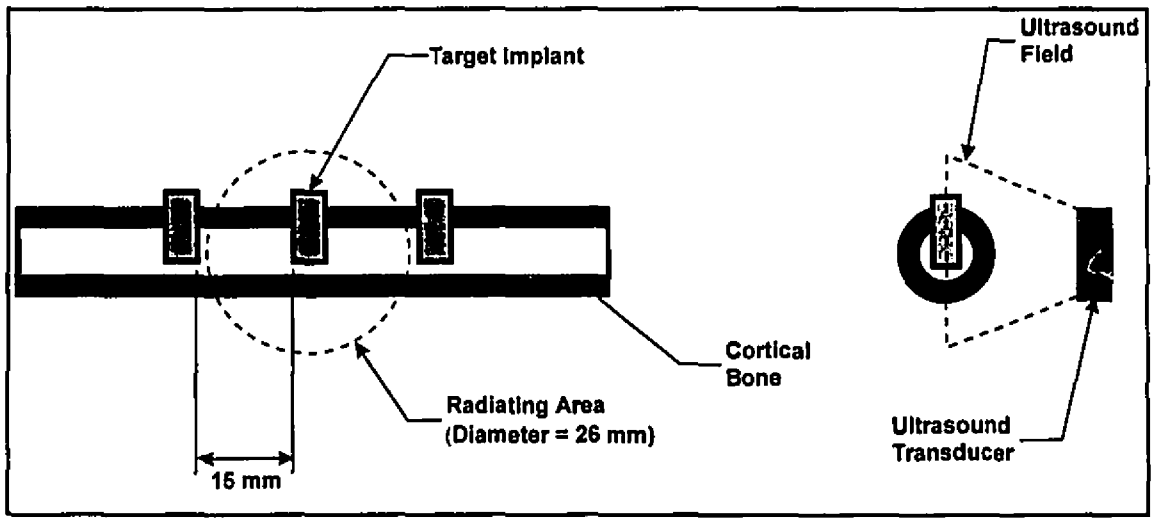



Figure 11. Schematic diagram illustrating the radiating area of the ultrasound signal with reference to implant placement.

The C-shaped drill jig was clamped around the shaft of the femur and tightened (Figure 12). The first bushing, corresponding to a 2.5 mm drill, was inserted into the bushing guide and a pilot hole was made with a battery driven drill (Mikita cordless driver drill, Mikita Electric Works, Ltd., Japan). Very slow drill speeds (0-250 RPM) were applied along with copious water irrigation to minimize mechanical and thermal trauma of bone at the drill site (Figure 13). Once the hole was made through the lateral cortex, the first bushing was removed and the second bushing, corresponding to a 4.95 mm drill, was inserted into the jig. The size of the drill was chosen in order to obtain a slight press fit between the implant and the bone. The diameter of the hole was enlarged to 4.95, again with adequate irrigation. Once the holes were made, care was taken to remove as little periosteum as possible while removing any debris that obstructed access of the implant to the hole.

Figure 12. The femoral clamp and drill guide placed in the wound.

Figure 13. A drill hole being made through the lateral cortex of the femur with application of constant water irrigation.

The implants were then inserted into the holes with the bevelled end first. They were gently tapped further into the holes using a rod and a mallet and were left approximately two millimetres proud of the lateral surface of the femur (Figure 14 and 15). Once all three implants were inserted, the wounds were irrigated and closed with absorbable sutures. Prior to closing, the skin was marked with an absorbable suture over the central implant, labelled as the "target" implant. The procedure was then repeated on the opposite femur with implants placed in the same portion of the femoral diaphysis. The femur that was operated on first was randomly chosen and served as the one to receive NILIUS treatment.

At the end of surgery the animals were given analgesics (Levodromoran 0.75-1.00 cc, 2 mg/mL, Hoffmann Laroche, Mississauga, Ont.) for the first 24 hours postoperatively, every eight hours. Following surgery the dogs were placed into one of two groups. One group underwent daily ultrasound treatment for two weeks and the other for three weeks. No activity restraints were imposed and the animals walked normally within two or three days postoperatively.

Figure 14. The implants were gently tapped into the drill holes with a rod and mallet.

Figure 15. The implants were left approximately 2 mm proud of the surface.

## Ultrasound Stimulation

Ultrasound stimulation began on the first day postoperatively. Each day prior to treatment, the dogs were anaesthetized with thiopental to ensure immobilization during stimulation. They were placed in the lateral decubitus position with the treatment side facing up. Copious ultrasound gel was applied to the skin at the marker representing the target implant and the transducer was taped to the skin over the anterior aspect of the femur (Figure 16). The treatment lasted for 40 minutes each day. The transducer was equipped with a timer which automatically terminated the signal after 40 minutes.


Figure 16. Ultrasound transducer (a) in place over the anterior aspect of the femur with copious ultrasound gel (b) applied to the skin.

The study by Tanzer et al. utilized 20 minutes of stimulation and indicated a modest positive effect of NILIUS on bone ingrowth. It was reasoned that the transcortical model should be studied in the context of additional stimulation time, to ascertain if increased energy input might further enhance the effect described by Tanzer et al. Doubling the time to 40 minutes was based on discussion with the transducer manufacturer (Exogen Inc.).

**Periods of Implantation**

The periods of implantation were chosen based on previous studies which demonstrated that short time periods, such as two and three weeks, are most useful in distinguishing the acceleration effects of bone ingrowth, or fracture healing, from a control (63,64). An additional consideration was that bone ingrowth is so rapid under the ideal healing conditions of the nonfunctional transcortical implant that maximum ingrowth is achieved by six to eight weeks following implantation. Therefore, slight differences in the rate or extent of bone ingrowth due to a particular treatment can be overlooked at longer periods of implantation (9).

## D. Specimen Preparation for Histology

### Embedding

At the end of the protocol periods of stimulation, the dogs were administered a lethal injection of barbiturates. The femora were extracted and stripped of soft tissue. The proximal and distal ends of each femur were removed with a cast saw and the remaining segment, containing the implants, was then radiographed in an anteroposterior view. The bones were prepared for backscatterred scanning electron microscopy (SEM) by the following protocol which involved dehydrating, degreasing, defatting, and embedding in polymethylmethacrylate (PMMA):

1) Small drill holes, one to two millimetres, were made in the bones surrounding the implants to ensure sufficient penetration of the various solutions into the bone. Care was taken not to come into contact with the implants.
2) The samples were then fixated in a 10% solution of formalin for 48 hours.
3) The bones then underwent dehydration in 70% ethanol for two days.
4) The bones were further dehydrated for 48 hours in 95% ethanol.
5) The specimens were then defatted and degreased in a 1:1 solution of acetone and ether for two days.
6) Dehydration was completed in 100% ethanol for another 48 hours.

7) The femora were immersed in liquid PMMA monomer, inhibited with 10 ppm methyl hydroquinone, and activated with 5 g/L of benzoyl peroxide. This solution was stored refrigerated to prevent premature polymerization.

8) The PMMA described above was partially polymerized by heating it in a water bath at 50°C for approximately 12 hours. Once the monomer had achieved the consistency of a thin syrup, the process was stopped by cooling under cold running water.

9) The femora were then placed in aluminum foil containers and covered with the PMMA solution. The aluminum containers were then placed in a vacuum chamber of approximately 70 mmHg in order to remove any trapped air. The vacuum was occasionally released to ensure that the specimens were constantly and completely embedded in the PMMA. After six to eight hours of vacuuming, the samples were left at room temperature to polymerize.

10) Once polymerization occurred, which took approximately eight hours, the samples were placed in a 35°C oven for one or two days to ensure that polymerization had occurred to completion. This process resulted in a block of PMMA, or plexiglass, that contained the femur with the transcortical implants.

**Sectioning**

Each block was then sectioned on a diamond blade low speed cut-off machine (Varicut, Leco Corp., Michigan) (Figure 17). The implants were carefully aligned so that they were sectioned through the center of their long axis. Each implant was divided into two

equal halves so that an evaluation of the amount of bone ingrowth could be obtained at the deepest region of the implant (Figure 18). This posed a potential problem in data analysis. At times there was difficulty obtaining a perfectly central cut through the implant. The most representative interface for quantitative analysis is at or near the implant centre. This allows evaluation of ingrowth across the full implant diameter. There is a tendency with transcortical implants for bone ingrowth to progressively develop from the cortical edges toward the centre. Thus, a section cut a distance away from the centre could give the illusion of greater depth of bone ingrowth than actually exists (Figure 19).

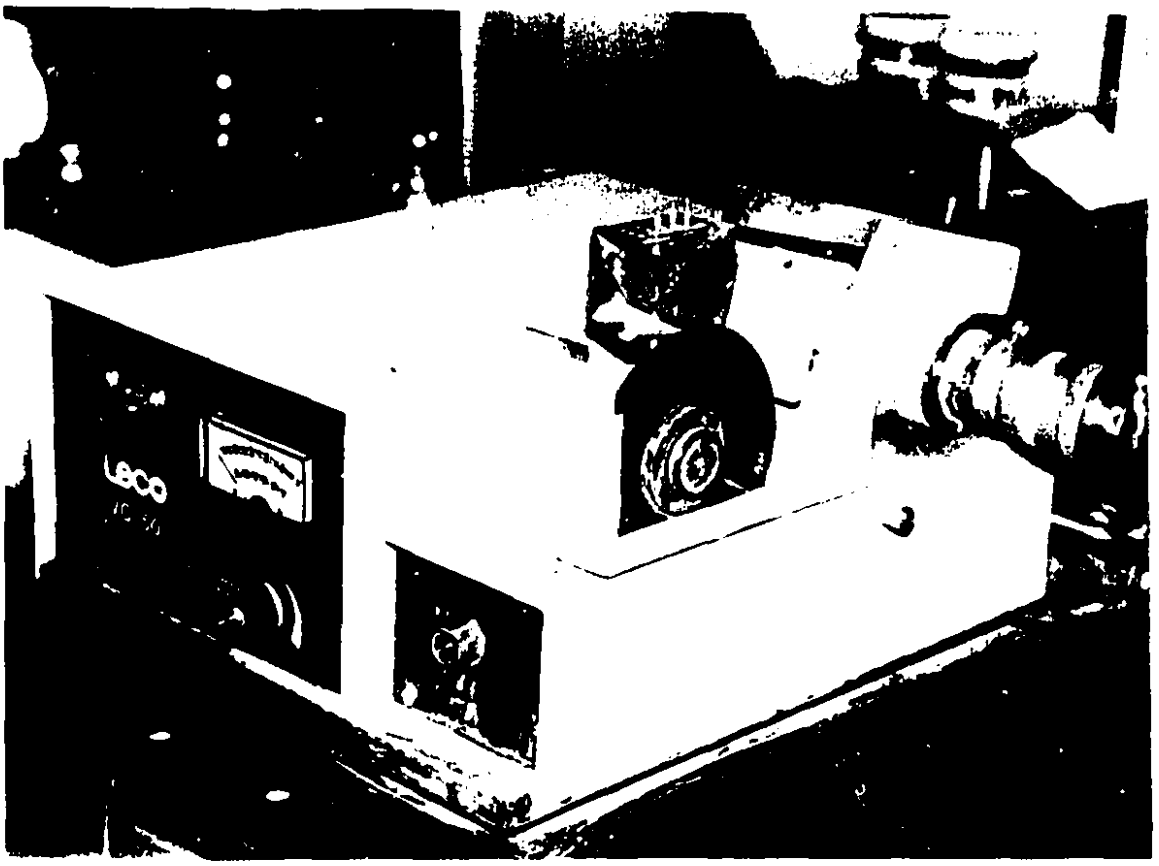



Figure 17. The vari-cut cut off machine with a sample held perpendicular to the blade by a vise. The diamond coated blade was 127 mm in diameter and 0.38 mm in thickness.

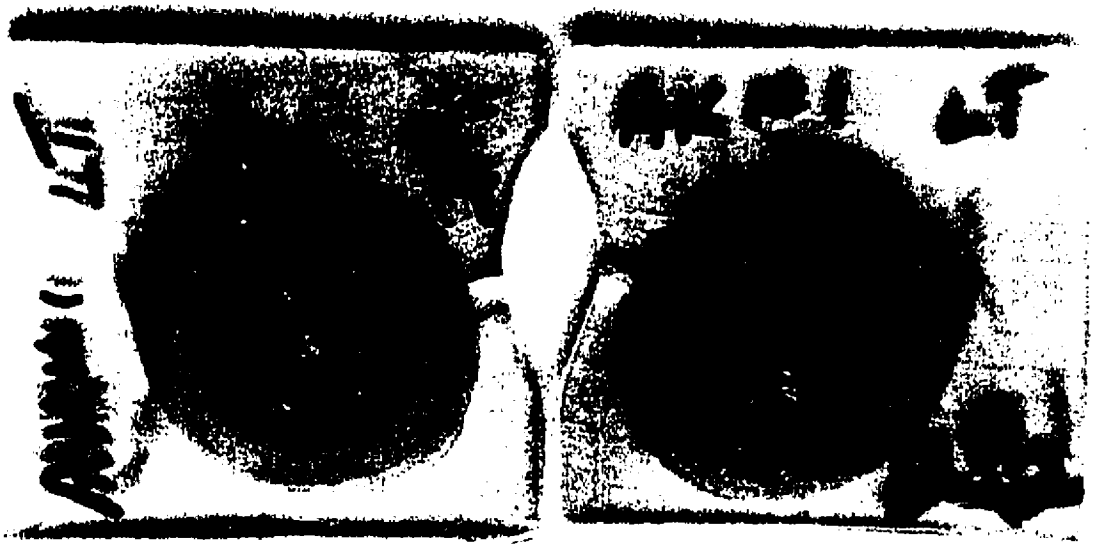


Figure 18. PMMA embedded sections cut through the longitudinal axis of the implant.

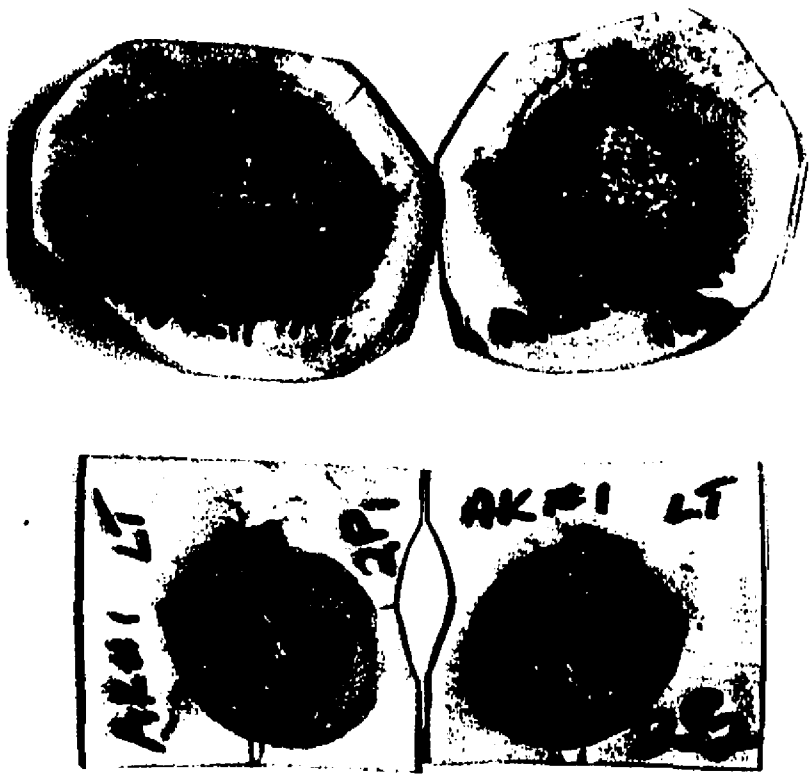



Figure 19. Comparison of tangential and central cuts through the implant. The top two sections were cut off-center and thus possess a smaller diameter than the two bottom, centrally cut sections.

Central cuts were not obtained due to one of two problems: One was "wandering" of the blade, or improper setup of the bone on the blade so that the center of the implant was not directly above it. The "wandering" of the blade was a result of the pressure exerted by the weight of the sample and slight looseness in the cutting assembly causing the blade to drift away from its original setting. The second problem was the 0.38 mm thickness of the blade which inevitably caused some sample loss.

Measures were taken in order to compensate for unequal sections. Considering that the diameter of the implants was five millimetres, it was decided that only cut specimens that had implant widths of 4.50 mm or greater would be accepted for analysis. When one half of the implant measured less than 4.50 mm it was not included in the analysis. In order to obtain two values per implant, the half measuring greater than 4.50 mm was re-polished until it measured at least 4.50 mm in diameter and then re-analyzed.

## E. Preparation for Backscatterred Electron Microscopy

The undecalcified, unstained, methylmethacrylate embedded, histological sections were first polished using abrasive paper of 120, 320 and 600 grit, under water irrigation, in preparation for backscattered SEM. The sections were polished further with 1.0 $\mu$m and 0.3 $\mu$m alumina (Figure 20). The sections were ultrasonically cleaned in 100% ethanol, air-dried, and sputter-coated with gold-palladium prior to mounting on a stage with electron conductive tape for viewing with scanning electron microscopy.

Figure 20. The polishing wheels used to prepare the samples for SEM

## F. Quantification of Bone Ingrowth

A density specific image of the bone-implant interface was obtained using the backscatterred electron mode on a JEOL 840 scanning electron microscope. The image was usually obtained with a magnification of 15 to 18 times, a working distance of 38 mm, and a 15 KeV beam. The techniques used were described by Holmes and later by Bloebaum et al. (92-94). The image obtained was from the most superficial two to three

microns of the sample. The image was photographed with 4" x 5" black and white Polaroid film.

The area of interest was defined by the endosteal and periosteal cortical bone edges, medially and laterally, and the edges of the implant, anteriorly and posteriorly. Regions that protruded above the periosteum or below the endosteum were excluded from the image analysis (Figure 21).

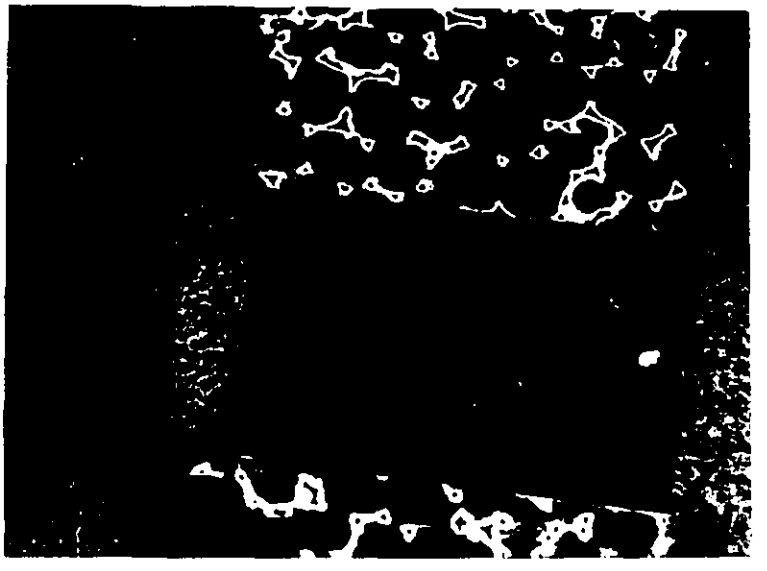


Figure 20. Scanning electron micrograph with the shaded parallelogram representing the area of interest as described previously.

Using computer image analysis (Tracor Northern, Middleton, WI) a horizontal register was digitized at 256 points. The resulting waveform demonstrated three different signal levels corresponding to metal, bone, and "other space". The waveform was used to set the brightness of each signal. The image was then digitized as a 256 x 256 array and the components were displayed as a histogram of frequency versus density. Each osteocyte lacuna was removed by a filtering technique which allocated all single or paired pixel codes to their neighbours. Artifacts, such as air and possible debris not eliminated previously during sonification, were removed simultaneously by the filtering. The computer was programmed to calculate the volume fraction percentage of each component and the percentage of bone ingrowth by the formula:

$$\% \text{ ingrowth} = \frac{\text{total-metal}}{\% \text{ bone}}$$

For each implant, two sections were scanned and averaged in order to give one value for the extent of bone growth into the implant.

## G. Statistical Analysis

The Wilcoxon Rank Sum Test was used to compare bone growth into the stimulated and control implants at both protocol implantation periods. It was also conducted to assess the bone ingrowth difference between the target implants and the control centre implants of the contralateral femur. An unpaired Student's t-test was conducted to assess the

difference between the target implants and the non-target stimulated implants. The ingrowth of the non-target implants was calculated by averaging the extent of bone ingrowth of the two implants adjacent to the target implant in each stimulated femur. An analysis of covariance (ANCOVA) was also performed in order to separate the overall effect of time and individual dog on bone ingrowth.

# IV. RESULTS

## A. Surgery

There were no complications intraoperatively. On the first postoperative day, one dog was lost from the study due to death during ultrasound stimulation. An autopsy was not performed, however, it was assumed that the death was caused by a reaction to the anaesthetic. One dog was not included in the study since it was determined to be skeletally immature preoperatively.

## B. Implants- Porosity Characterization

The mean implant porosity determined from 52 randomly chosen scanning electron micrographs was $73.9 \pm 3.0\%$. The range of porosity was between 65.9% and 80.2%. The pore size was measured by applying a linear intercept method to scanning electron micrographs. The distance between adjacent metal struts was measured on 500 randomly selected pores and averaged $655 \pm 146$ $\mu$m.

## C. Implants- Description of Bone Ingrowth

Seventy-two implants were analyzed. The bone grew into the interconnecting pores formed by the metallic struts of the implant. Bone was usually observed to be ingrown

from the intramedullary canal and seldom from the cortical edges of the bone (Figure 22). When small amounts of bone were ingrown (ie. < 10%) the origin appeared to be the endosteal cortical edges closest to the anterior and posterior surfaces of the implants (Figure 23). A periosteal reaction, resembling callus formation on the periosteal surface of the femora abutting the edges of the implant, was observed in 36 of the implants (Figure 24). There was no greater tendency for a periosteal reaction in either the stimulated or the control femora. When a periosteal reaction was present, however, some bone was observed to be grown into the implants from the periosteal surface. No other differences in the origin of bone ingrowth were observed between the two and three week dogs.

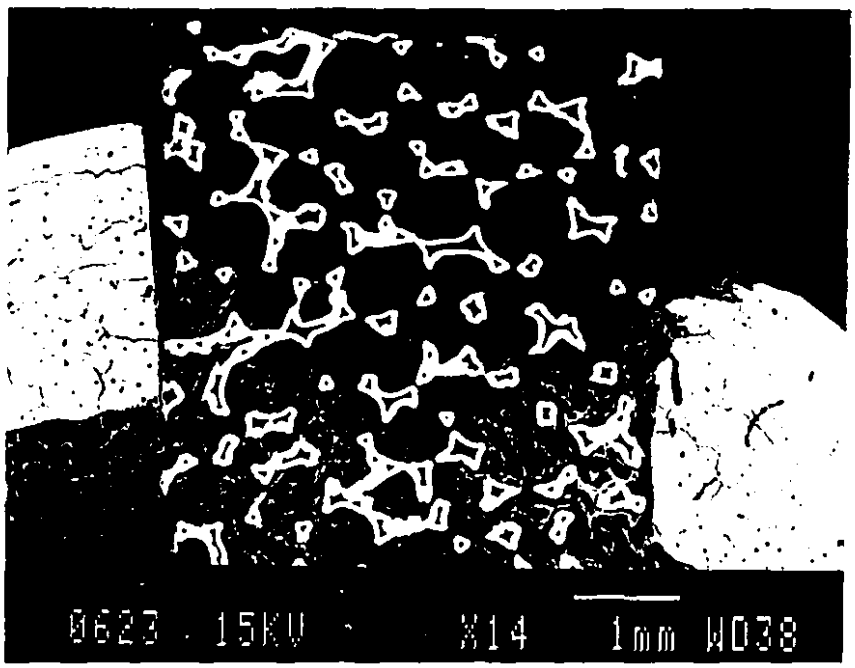



Figure 22. Scanning electron micrograph illustrating bone ingrowth originating from the endosteal region.

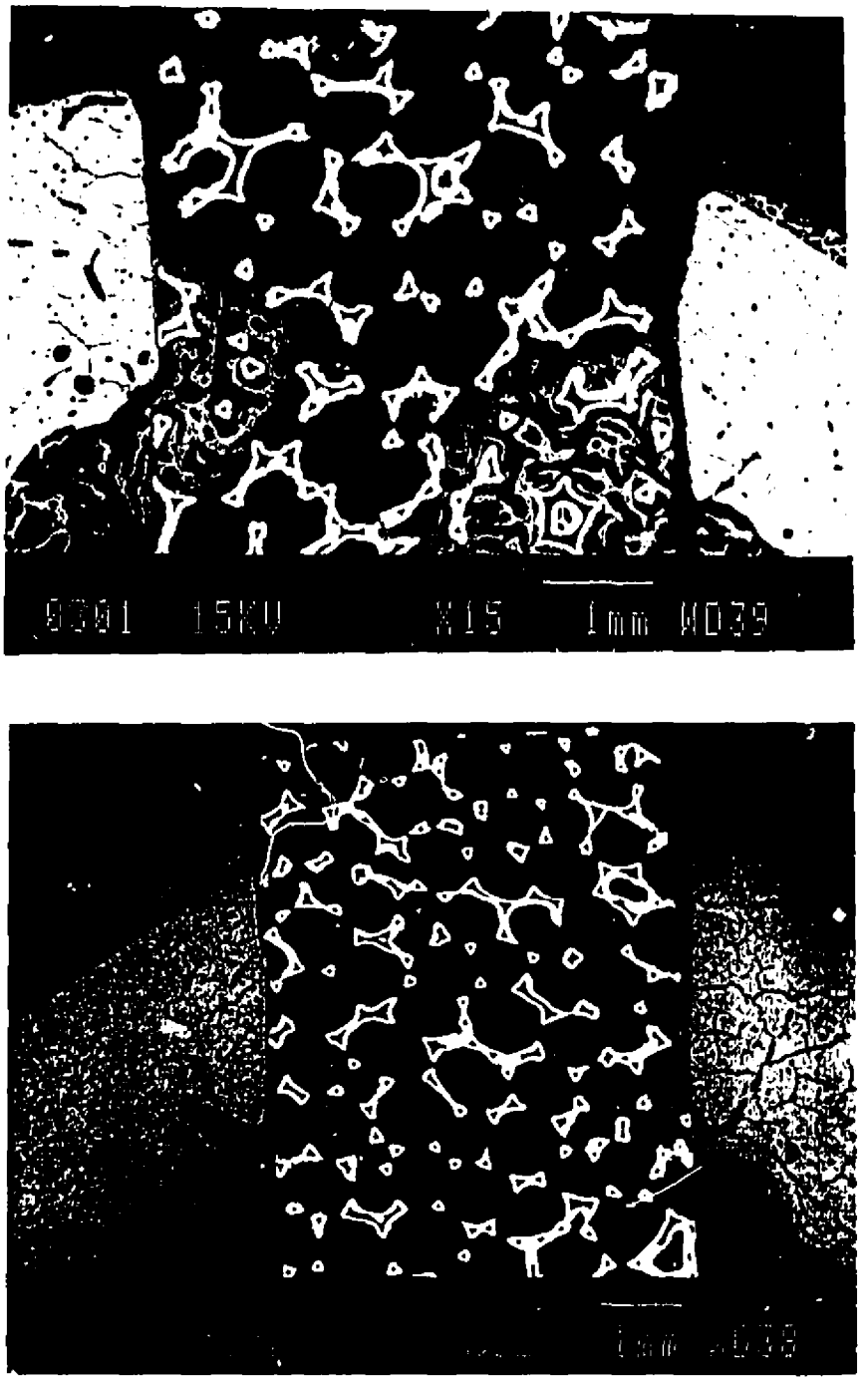



Figure 23. Scanning electron micrographs illustrating the origin of bone when little amounts of growth into the implants (ie. < 10%) were observed.

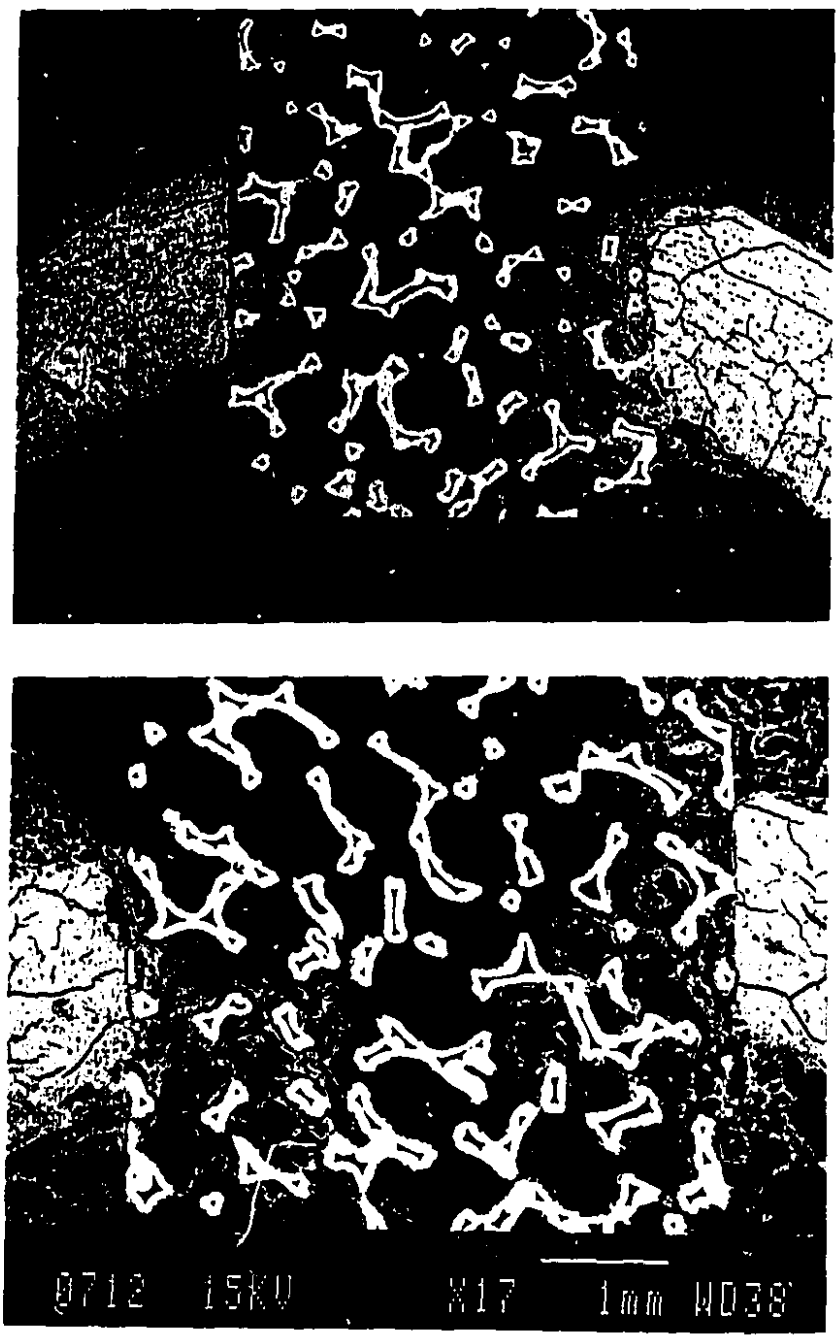



Figure 24. Scanning electron micrographs demonstrating bone growth into the implants with a periosteal reaction.

D. Bone Ingrowth- Quantitative Analysis

The percentage of bone growth into the available space of each implant was compared. The two variables chosen for analysis were period of implantation and treatment protocol. Data were separately analyzed for the individual implants which served as the ultrasound target and were compared to the central control implant of the contralateral femur and to the remaining two implants of the stimulated femora. As a result there were eight subsets of data:

1) Two week femora with ultrasound stimulation.

2) Two week control femora.

3) Three week femora with ultrasound stimulation.

4) Three week control femora.

5) Two week target implants.

6) Two week stinulated non-target implants.

7) Three week target implants.

8) Three week stimulated non-target implants.

E. Period of Implantation

Data were compared between dogs stimulated for two weeks and those stimulated for three weeks. There was a total of 36 implants per time period, half of which received ultrasound stimulation. The femora that were stimulated for two weeks demonstrated $12.4 \pm 5.3\%$ bone ingrowth as compared to the femora that were stimulated for three weeks which had a mean of $21.1 \pm 6.5\%$ ingrowth. The control femora of the two week dogs and three week dogs had a mean ingrowth of $12.7 \pm 6.5\%$ and $22.7 \pm 7.3\%$, respectively.

Both individual dog ($p < 0.001$) and time ($p < 0.001$) had an effect on the amount of bone ingrowth, overall. After separating out the effect of each dog and time interval, ultrasound did not have a stimulatory effect on the rate and extent of bone growth into porous metallic implants ($p = 0.81$).

F. 2 Week Analysis

The two week data are listed in Table 2. The extent of bone growth into the implants of the stimulated and control femora of the two week dogs was $12.4 \pm 5.3\%$ and $12.7 \pm 6.5\%$ respectively (Wilcoxon Rank Sum, $p = 0.74$) (Figure 25). Four of the six compared femora had greater bone growth in the control implants than the stimulated implants. The stimulated target implants had a mean ingrowth of $10.6 \pm 6.8\%$ as compared

to the contralateral, centrally placed, control implants which had 15.7±8.4% (Wilcoxon Rank Sum, p=0.12). Four of the six central implants from the control femora had greater bone ingrowth than the contralateral stimulated target implants. The bone ingrowth of the two week stimulated target implants was compared with the non-target stimulated implants which had a mean of 13.3±4.5% bone ingrowth (Student's t-test, p=0.25).

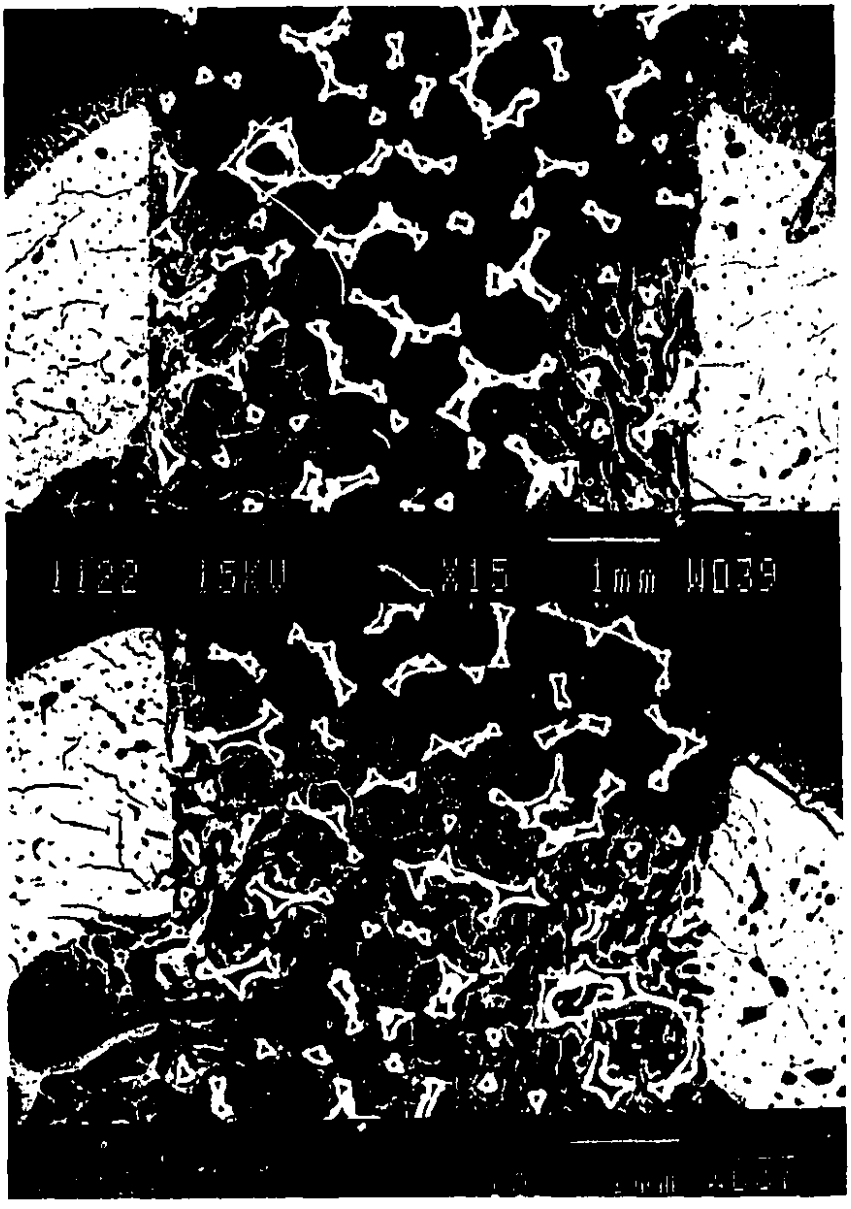



Figure 25. Comparison of bone ingrowth at 2 weeks in a stimulated implant (top) with 12.9% bone ingrowth and control implant (bottom) with 16.0%.

Table 2 Mean Percentage of Bone Growth into the 2 Week Implants

| Dog# | Stimulated | | | | Control | | | |
|---|---|---|---|---|---|---|---|---|
| | 1p target | 2p target | 3p target | Average | 1p control target | 2p control target | 3p control target | Average |
| 1 | 14.4 | 8.1 | 9.5 | 10.7 | 3.8 | 7.3 | 4.9 | 5.3 |
| 2 | 13.0 | 0.28 | 6.8 | 6.7 | 10.2 | 10.6 | 3.0 | 7.9 |
| 3 | 18.2 | 14.2 | 17.4 | 16.6 | 15.4 | 23.8 | 15.9 | 18.4 |
| 4 | 15.1 | 18.8 | 20.2 | 18.0 | 14.8 | 28.0 | 17.7 | 20.2 |
| 5 | 10.0 | 6.9 | 6.8 | 7.9 | 12.0 | 9.2 | 9.4 | 10.2 |
| 6 | 17.6 | 15.3 | 10.7 | 14.6 | 13.6 | 15.2 | 13.9 | 14.2 |
| Average | **12.4±5.3** | | | | **12.7±6.5** | | | |

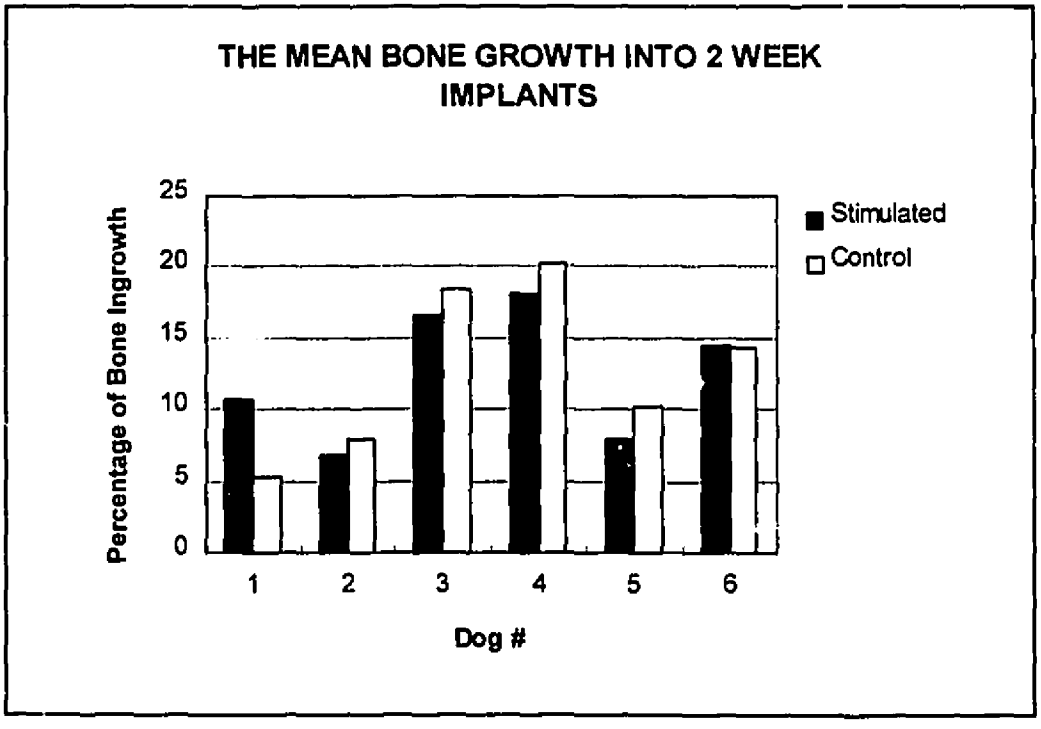
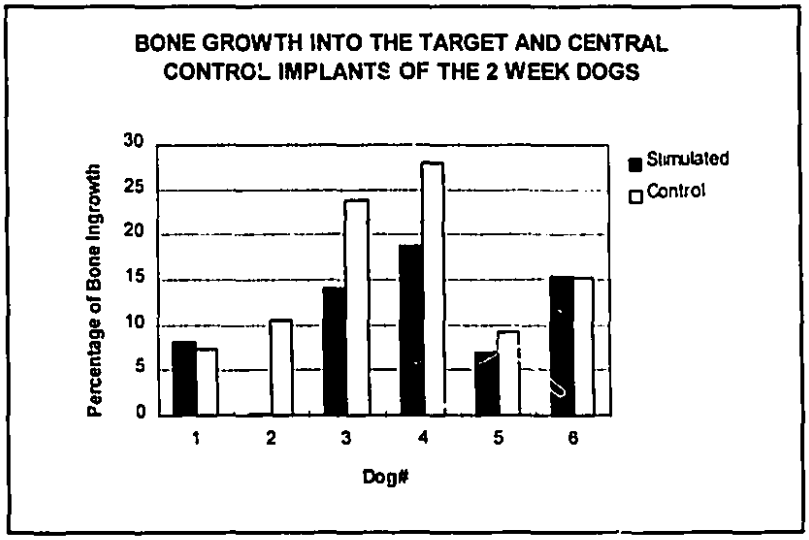


Table 3 Mean Percentage of Growth into the Target Implants of the 2 Week Dogs

| Dog# | Stimulated | Control |
|---|---|---|
| 1 | 8.1 | 7.3 |
| 2 | 0.28 | 10.6 |
| 3 | 14.2 | 23.8 |
| 4 | 18.8 | 28.0 |
| 5 | 6.9 | 9.2 |
| 6 | 15.3 | 15.2 |
| Average | 10.6±6.8 | 15.7±8.4 |



G. 3 Week Analysis

The three week data are listed in Table 4. Thirty-six implants were analyzed at three weeks. The mean ingrowth for the stimulated implants was 21.1±6.5% compared to the control femora which had a mean ingrowth of 22.7±7.3% (Wilcoxon Rank Sum, p=0.53). Three of the six control femora had greater means of bone ingrowth than the contralateral stimulated femora. The stimulated target implants had a mean percentage ingrowth of 19.1±5.1% as compared to the central control implants of the contralateral femora which had a mean of 24.5±8.0% (Wilcoxon Rank Sum, p=0.12) (Figure 26). Four of the six central control implants had greater bone ingrowth than the stimulated target implants. The mean ingrowth of the non-target stimulated implants was 22.0±7.1% which was not significantly different from the target implants (24.5±8.0%) (Student's t-test, p=0.25).

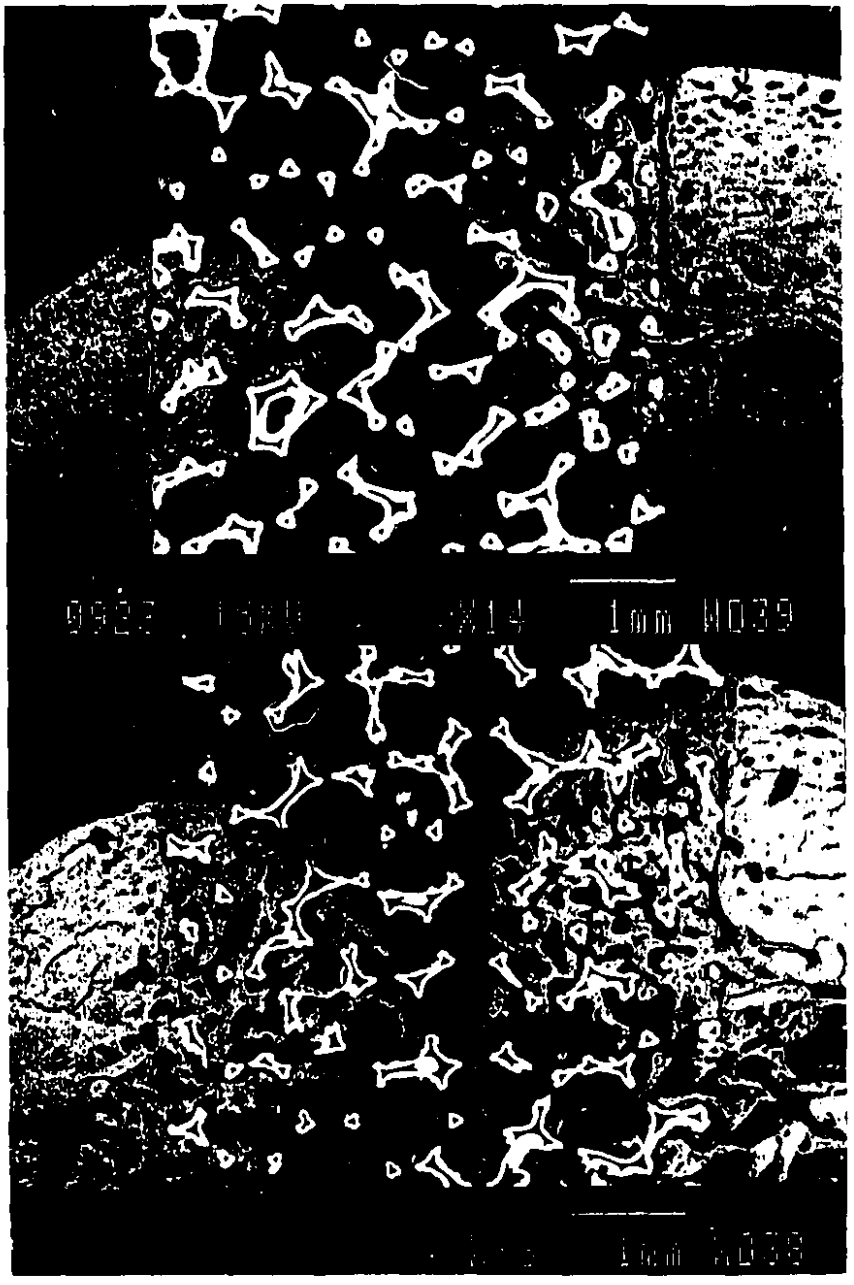



Figure 26. Comparison of bone growth into the target stimulated implant (top) with 23.6% bone ingrowth and the central control implant (bottom) with 30.5% at 3 weeks.

Table 4 Mean Percentage of Bone Growth into 3 Week Implants

| Dog# | Stimulated | | | | Control | | | |
|---|---|---|---|---|---|---|---|---|
| | 1p | 2p | 3p | Average | 1p | 2p | 3p | Average |
| | target | | | | control target | | | |
| 1 | 22.7 | 15.6 | 15.1 | 17.8 | 19.7 | 14.9 | 15.1 | 16.6 |
| 2 | 20.6 | 18.7 | 16.9 | 18.7 | 21.2 | 17.6 | 12.9 | 17.3 |
| 3 | 20.6 | 27.1 | 24.9 | 24.2 | 18.3 | 35.4 | 17.5 | 23.7 |
| 4 | 26.5 | 15.7 | 21.5 | 21.3 | 16.8 | 28.0 | 28.9 | 24.6 |
| 5 | 38.1 | 23.6 | 19.7 | 27.1 | 36.9 | 30.5 | 30.6 | 32.6 |
| 6 | 9.6 | 14.2 | 27.7 | 17.2 | 19.1 | 20.8 | 23.7 | 21.2 |
| Average | 21.1±6.5 | | | | 22.7±7.3 | | | |

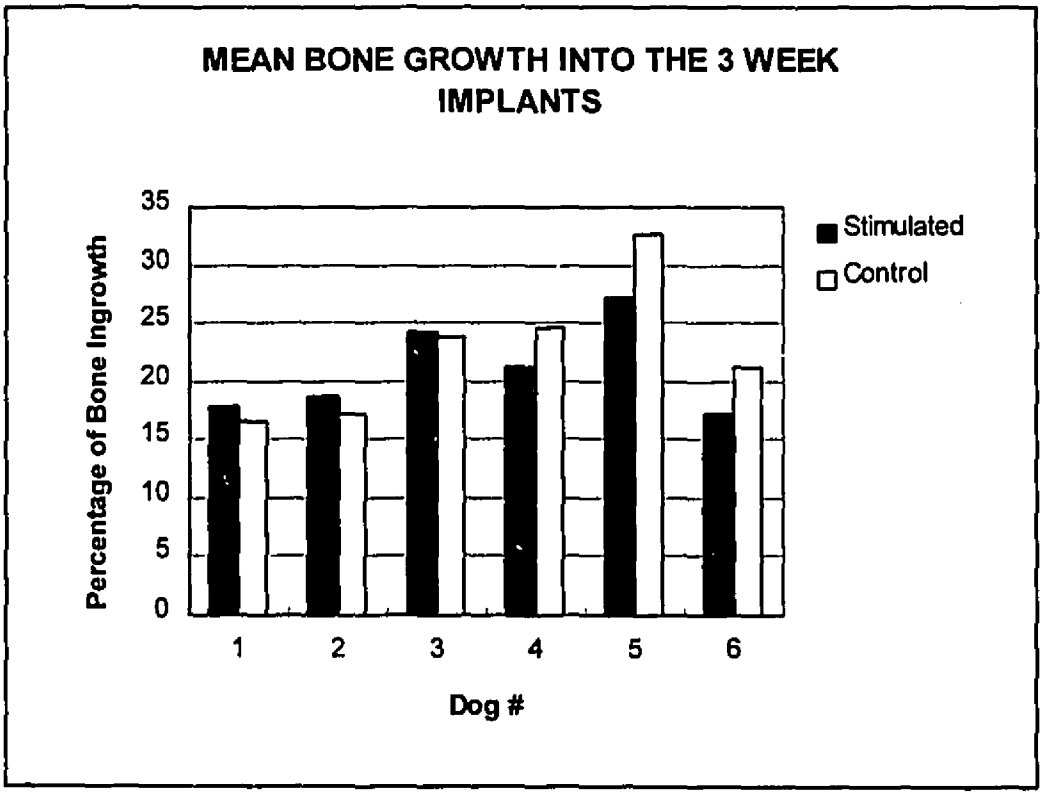
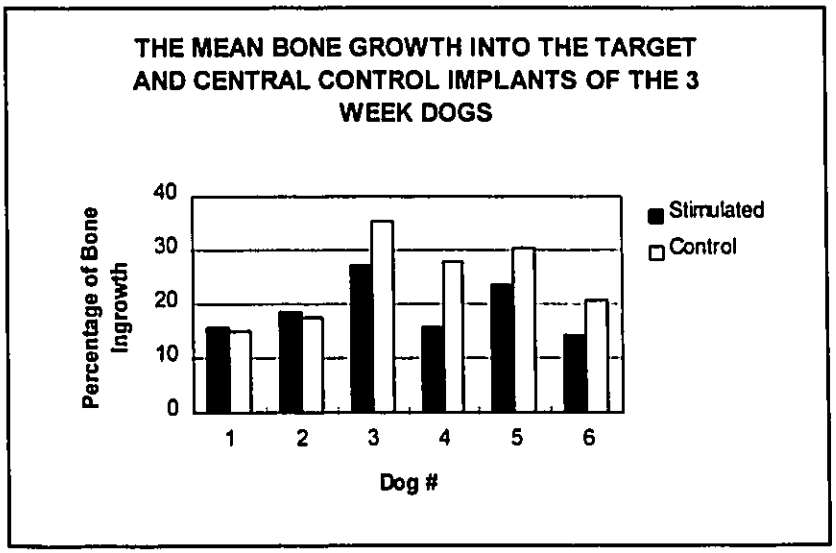


Table 5 Mean Bone Growth into 3 Week Target Implants

| Dog# | Stimulated | Control |
|---|---|---|
| 1 | 15.6 | 14.9 |
| 2 | 18.6 | 17.6 |
| 3 | 27.1 | 35.4 |
| 4 | 15.7 | 28.0 |
| 5 | 23.6 | 30.5 |
| 6 | 14.2 | 20.8 |
| Average | 19.1±5.1 | 24.5±8.0 |



# V. DISCUSSION

This study was primarily designed to ascertain if additional ultrasound stimulation time beyond the 20 minutes originally used by Tanzer et al. would have a positive effect on enhancing bone growth into porous coated implants. The results clearly suggest that 40 consecutive minutes of NILIUS stimulation does not have a stimulatory effect on the rate and extent of bone growth into porous tantalum implants at two and three weeks.

For example, the overall data treatment by ANCOVA indicated the effect of NILIUS treatment to be significant at the $p=0.8$ level, indicating no statistical difference between stimulated and control implants. Analyzed individually at two and three weeks, the data indicate that the difference between the stimulated and control implants was not statistically significant either ($p=0.74$ and $p=0.53$, respectively). At both time periods, the difference in bone ingrowth between the target and central control implants, however, was significant at the $p=0.12$ level, suggesting that there was a trend toward suppression of bone ingrowth in the target implants as compared with the control central implants.

The difference in the amount of bone growth into the target implants and the non-target stimulated implants, at two and three weeks, was compared in order to assess the effect of distance from the transducer. The non-target implants had more bone ingrowth than the target implants at both time periods but with relatively high ($p=0.25$) significance levels. This finding suggests that although not all implants were within the NILIUS field, they were still

affected by the stimulation probably due to propagation of the ultrasound energy within the bone. However, concern regarding the accuracy of transducer placement must also be addressed as a possible cause for this finding. There may have been slight variation in daily stimulation with respect to accurate placement of the transducer over the central implant. A possible cause for not placing the transducer directly over the target is due to the fact that the marker representing the target implant was placed on the skin which moves slightly relative to the underlying bone. A second possible cause for not directly stimulating the target implant is that intraoperatively the marker was inaccurately placed on the skin. Inaccurate placement of the transducer over the target implant may, therefore, have caused inappropriate comparison of the stimulated and nonstimulated implants, especially between the target implants and the centrally placed control implants.

Possible shortcomings of this study also include the method of cutting the sections and the absence of mechanical analysis. In addition to cutting the implants longitudinally through their central axis to determine the amount of bone growth into the implants, it might be helpful to analyze cross-sectional cuts to determine the differences in the amount of bone ingrowth from different regions of the cortical bone. Mechanical testing was not conducted on the implants in this study. The advantage to conducting mechanical evaluation by push-out testing is the opportunity to collect additional data regarding the strength of fixation of bone to the implants. Given similar amounts of bone at the porous implant interfaces, it is possible that bone formed with and without ultrasound stimulation might have different mechanical properties and thereby give rise to different shear strength measurements. Future studies of this type should,

therefore, include mechanical testing to assess the difference between ultrasound stimulated and control samples.

The protocol implantation periods for this study were chosen based on previous investigations which have demonstrated that ultrasound stimulation has its greatest effect on bone growth in the first two to three weeks postoperatively, or following injury. Duarte found that the stimulatory effect of ultrasound on fracture healing in rabbits was greatest in the first 10-12 days (67). Pilla found the greatest effect on fracture healing to be between days 14 and 23 from initiation of stimulation, also in rabbits (64). Tanzer et al. found that ultrasound increased the amount of bone ingrowth over the entire implantation period in dogs, however, its greatest effect was also within the first two or three weeks of treatment (63).

Previously, only one study has been conducted to investigate the effect of non-invasive, low intensity, pulsed ultrasound on bone growth into porous metallic implants. Tanzer et al. studied the effect of daily 20 minute ultrasound stimulation on bone growth into fully porous titanium metal implants for periods of two, three, and four weeks (63). The pore size of the implants ranged from 100-350 $\mu$m with a mean of $274 \pm 37$ $\mu$m. An increase of bone ingrowth in the ultrasound stimulated implants was observed at each individual time period. In total, there were 22 matched pairs of implants. Seventeen of the 22 matched pairs had greater ingrowth in the stimulated implants, whereas in the present study 23 of the 36 matched pairs had greater bone growth in the control implants. Twelve of 18 were greater at two weeks and 11 of 18 were greater at three weeks. Eleven of the 12 target implants also demonstrated more

bone ingrowth than the equivalently placed implant of the contralateral femur in the study by Tanzer et al.. Almost the opposite result was found in the present study where ten of the 12 central control implants had greater bone ingrowth than the target stimulated implants.

The ultrasound signal parameters (intensity, frequency, radiating area, and depth of penetration) used in the study by Tanzer et al. were identical to those used in the present study (63). Three variables, however, were altered in this study. The material was changed from titanium to tantalum, the average pore size increased from $274 \pm 37$ $\mu$m to $655 \pm 146$ $\mu$m, and the time of stimulation was increased from 20 to 40 minutes. Each of these must be considered as possible factors influencing the difference in the results between the two studies.

Tantalum has been shown to be extremely biocompatible in various biomaterial applications, in addition to orthopaedics. It possesses lower corrosion current density and higher corrosion resistance than titanium and Ti6Al4V (76). It has been used in cardiology, for example, in pacemaker electrodes, and in neurology, for nerve repair (77,79,95). It has also been demonstrated that tantalum does not inhibit bone ingrowth. Osseointegration has been demonstrated into tantalum implants in dental and orthopaedic applications under unloaded and heavily loaded conditions for periods as long as eight to 12 years (82-84). Since tantalum is an excellent biocompatible material, at least as corrosion resistant as titanium, it is unlikely to have been a causal factor in the different results of the present study and that of Tanzer et al., especially in view of the short implantation periods.

The second potential influencing factor was the pore size. It has been determined that for bone ingrowth to occur the ideal pore size is in the approximate range of 50-400 $\mu$m (26-28). It should be noted that these are not strict limits since bone ingrowth has been documented when the pore size is above or below this range (28,96,97). The mean pore size of the implants used in this study was larger than the pore size typically used in porous coated joint replacement prostheses. However, Stackpool et al. recently conducted an evaluation of bone ingrowth using the identical implants of the present study and found 52% ingrowth at 4 weeks and 71% ingrowth at 16 and 52 weeks (86). Therefore, it is apparent that extensive bone ingrowth can occur with the tantalum implants even though the pore size exceeds the commonly accepted limits.

It is interesting to compare the control bone ingrowth data from Tanzer's study, using beaded titanium implants, with the present study and that of Stackpool et al. that used the identical tantalum implants as the present study (Table 6). The control tantalum implants in this study demonstrated $14.7 \pm 7.9\%$ and $22.7 \pm 7.3\%$ bone ingrowth at two and three weeks, respectively, while the control beaded titanium implants in the study by Tanzer et al. had $20.8 \pm 11.8\%$ and $34.1 \pm 8.8\%$ bone ingrowth at two and three weeks, respectively. The increased bone ingrowth at two weeks and three weeks in Tanzer's study was significant at the $p=0.1$ and $p<0.01$ levels, respectively (unpaired Student's t-test), suggesting some difference in early tissue response between the two types of porous materials. A different result arises when comparing four week control data between Stackpool's study and Tanzer's study. At four

weeks there was 51.7±8.5% and 38.2±8.0% bone ingrowth in Stackpool's and Tanzer's implants, respectively, a difference that was highly statistically significant at the $p<0.001$ level (unpaired Student's t-test).

Table 6. Mean and Standard Deviations from Control Data of Two Different Implants

| | 2 week control | 3 week control | 4 week control |
|---|---|---|---|
| Titanium (ref. 63) | 20.8±11.8, n=8 | 34.07±8.8, n=6 | 38.2±8.0, n=8 |
| Tantalum | 14.7±7.9, n=18 | 22.7±7.3, n=18 | 51.7±8.5, n=38 (ref.86) |

The third, and probably most significant, variation from Tanzer's study was the time of exposure to NILIUS. There have been no studies with an ultrasound stimulation time greater than 20 minutes per day. Pilla et al. (64), Heckman, et al. (65,66), and Duarte (67) demonstrated an accelerating effect of ultrasound on fracture healing, with stimulation times not exceeding 20 minutes per day. Knoch and Klug found a stimulatory effect in rabbits with as little as two minutes of daily treatment (37). Tanzer et al. demonstrated that 20 minutes of ultrasound stimulation resulted in an 18% relative increase in the extent and rate of bone growth into implants made of sintered titanium beads (63). Based on all considerations, it is most likely that the increase in stimulation time from 20 minutes to 40 minutes was responsible for the absence of enhanced bone ingrowth in the NILIUS treated implants. This may need to be further verified with additional studies of this type. For the immediate future, studies on

the effect of NILIUS on bone ingrowth should probably not be conducted with more than 20 minutes of daily stimulation.

The mechanism by which low intensity ultrasound accelerates fracture healing, or bone ingrowth, remains unknown. As an ultrasound wave travels through the tissue, its intensity decreases due to the conversion of sonic energy into heat, resulting in a slight local increase in temperature. This thermal effect has been speculated as a possible mechanism of action of ultrasound. Nonthermal effects are also theorized to be the mechanism of action for ultrasound stimulation of bone repair. It has been postulated that vibration, or pressure waves, induced by ultrasound, alter cell membrane permeability by causing mechanical deformation of the cell, or alternatively, creating an electrical effect (68). Yang et al. have suggested that ultrasound stimulation modifies noncollagenous protein synthesis or the expression of collagen isotypes (72). An understanding of the mechanism of action of ultrasound on bone growth may provide the necessary specifications in terms of time of stimulation, frequency, and intensity so that a maximal effect can be achieved.

After reviewing the literature of the various modalities for enhancing bone growth into porous metallic implants, including allografts, autografts, fibrin glue, periosteal activation agent, TCP, HA, PEMF, and direct electrical current stimulation, it is clear that there remains a need for a reliable, consistent modality. Non-invasive low intensity pulsed ultrasound has demonstrated to be effective in accelerating fracture healing in various experimental and clinical studies and has already received Food and Drug Administration approval for its use in that

capacity. It has also recently shown to be effective for a modest stimulation of the rate and extent of bone ingrowth, given the appropriate application time. Because NILIUS is non-invasive and does not require the addition of an implant coating or the inclusion of an osteoconductive substance, it could potentially represent a simple, convenient, and cost-effective method of improving the reliability of cementless total joint arthroplasty.

For NILIUS to have a meaningful clinical impact, however, it would probably have to demonstrate greater effectiveness in increasing bone ingrowth than the extent demonstrated by Tanzer et al.. In revision arthroplasty surgery where there are often appositional gaps between the implant and host bone and less bone stock, a modest increase in bone ingrowth may be sufficient for improving clinical results. The effect of NILIUS should be investigated in the presence of gaps and in models with compromised bone stock. Studies should also be conducted using an intramedullary model that is more representative of a joint replacement prosthesis. Depending on the results of these studies, it may be necessary to evaluate NILIUS in total joint replacement animal models, prior to consideration of studies in humans.

# CONCLUSION

This study has been successful in generating bone ingrowth data on a new porous orthopaedic biomaterial made of tantalum. The data show comparable ingrowth percentages compared with titanium and cobalt-chromium implants. More significantly, in the context of non-invasive, low intensity, pulsed ultrasound, this study revealed that 40 minutes of stimulation does not have the stimulatory effect on bone ingrowth at two and three weeks as revealed by a previous study with 20 minutes of daily stimulation. Some of the data suggest that there may be a trend toward suppression of bone ingrowth as a result of overstimulation. As additional studies in this field are pursued to evaluate the potential effectiveness of NILIUS, this finding serves as a valuable guideline for the planning of experimental protocols in terms of the time of stimulation that is most effective at enhancing the rate and extent of bone growth into porous coated implants.

# APPENDIX I

The amplitude of motion for a given particle within an ultrasound wave is very small and is intensity dependent. The displacement of particles within a cell does not exceed 1% of the cell's diameter and its velocity is found to be independent of the frequency. As a result of the high frequency of ultrasound, the vibrating particles are forced to change their direction (37,68).

In a plane travelling wave the radiation force is in the direction of wave propagation and is proportional to the intensity. In the case of biological cells, movement is towards the pressure minimum nearest them. As a result, cells become concentrated in a series of planes one half the wavelength apart. The intensity reported to cause this banding is in the vicinity of 1 $W/cm^2$, a level typical of ultrasound therapy (68).

Pulsed ultrasound, as opposed to continuous ultrasound, is often chosen for therapeutic applications. Continuous ultrasound applies to waves that are transmitted uninterrupted, resulting in constant energy application to the medium being insonated. As a result, there are no breaks from the "internal tissue massage." With continuous ultrasound, problems arise when higher doses are applied, the most notable being the generation of excessive heat. Pulsed ultrasound is an option that prevents these dangers (37). When pulsed ultrasound is used, frequencies other than the central frequency are present. The range from the lowest to highest

frequency is known as the bandwidth.

In 1982, Nyborg conducted a study and described the effect of low intensity ultrasound, of the lower megahertz frequency, on biological cells and tissues, where small gas-filled channels or pores are present. When these bodies are stimulated, they act on the surrounding medium in the form of "unique" radiation forces, pressure, and torque. In liquids, microstreaming, or small-scale eddying is produced. A combination of these forces is hypothesized by Nyborg to be the mechanism of action of ultrasound on biological cells and tissues (99).

Lehmann and De Lateur listed the following favourable effects of heat therapy in which tissue temperature was maintained at 40-45$^0$C for 5-30 minutes (100):

1.Extensibility of collagen was increased.

2.Joint stiffness was decreased.

3.Pain relief was produced.

4.Muscle spasms were relieved.

5.Resolution of inflammatory infiltrates, edema, and exudates occurred.

6.Blood flow increased

Cavitation has been defined as "any observable activity involving a bubble or a population of bubbles stimulated into motion by an acoustic field" (101). The acoustic energy is concentrated into high stresses, elevated temperatures, and/or fluid velocities which have the potential to affect cellular activity. The cavitation which is most likely to be involved causes gas bubbles, a few microns in size, to oscillate in a regular fashion for many acoustic cycles. As a result, microstreaming is enhanced and may be responsible, at least in part, for the observed changes in cell membrane permeability to ions such as sodium and calcium.

In 1968 Friedenberg and Kohanin demonstrated that live, nonstressed bone possesses a permanent direct current polarization which is dependent on cellular activity (102). Areas with high activity, such as the metaphyses, are electronegative in comparison to areas that are less active, such as the diaphyses.

The piezoelectric properties of bone as described by Fukada and Yasuda in 1957 refer to the electrical potentials acted upon by mechanical tension, compression, shear stress, and torsion (103). When a bone is deformed by mechanical means, two opposite charges develop at the end of the electrical axis. Those areas that are experiencing compression become electronegative, while those experiencing tension become electropositive. It is generally believed that the piezoelectric effect of ultrasound is a result of the mechanical shearing action of collagen fibres and an associated deformation at the molecular level of hydrogen bonds (104,105).

# APPENDIX II

There are a variety of techniques used in order to apply a metal coating to a substrate. These include physical vapour deposition (CVD), electroplating, plasma spraying, and sputtering. Chemical vapour deposition, however, is a technique that is not limited by a factor which affects all of the other techniques, that is its ability to deposit a coating in an area that is not directly visible to the source. With the CVD technique, a solid material is deposited onto a substrate by means of thermally activated chemical reactions. Since both the products and the reactants are transported in the vapour phase, the technique is useful for coating complex shapes, infiltrating porous materials, and coating fine particles (106).

CVD offers many advantages over the other deposition processes. Firstly, the process can occur at temperatures well below the melting point of the material being applied. Secondly, the technique is applicable to a variety of materials. And, lastly, because the temperature remains well below the melting point/decomposition temperature, it is possible to apply CVD to a variety of substrates (106).

Chemical vapour infiltration (CVI), a variant of CVD, is a technique whereby there is deposition within the surface of a porous substrate, as opposed to simply on the surface. The infiltration is very slow in order to infiltrate material into small pores without closing the porosity (106).

The process of CVI begins with the pyrolysis of a thermosetting polymer foam precursor in order to obtain a carbonaceous skeleton with 10-1000 pores per linear inch. The skeleton possesses a repeated and interconnected dodecahedron array. This structure is then infiltrated by CVD/CVI. CVI allows 10 to 100 $\mu$ of the material to be deposited onto the interior surface of the carbon skeleton which greatly enhances its structural integrity. The properties of the composite are dominated by the material, in this case, tantalum, providing exceptional stiffness and strength with the addition of very little weight. The resulting mechanical properties are usually one or two orders of magnitude higher than the bulk material since the deposited material is usually 100% dense (106).

In order for tantalum infiltration to occur it must first be chlorinated to form tantalum pentachloride ($TaCl_5$). $TaCl_5$ then undergoes hydrogen reduction upon deposition, producing a side-product of HCl. The substrate that is used for porous tantalum fabrication is vitreous carbon with a high void volume (97%) and a high surface area (106).

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