SECTION VII

PUBLISHED/UNPUBLISHED CLINICAL RESULTS

A. Unpublished Clinical Studies

Device Descriptions

The metal/metal (experimental) and metal/polyethylene (control) devices in this clinical summary report are all semi-constrained total hip prostheses from three orthopaedic device manufacturers.

The metal/metal acetabular components are two-piece modular components consisting of 28 mm, 32mm and 36mm inner diameter cobalt chromium molybdenum (Co-Cr-Mo) alloy bearing inserts fitted to the outer shells by means of a taper fit mechanism. The outer rims of the bearing inserts are either neutral or have extended lips to provide for additional coverage of the modular femoral heads. The metal outer shells are manufactured from either commercially pure (CP) titanium or titanium alloy (Ti-6Al-4V). The outer surfaces of the acetabular components have either sintered or plasma sprayed porous coatings to provide for biological ingrowth as a means for primary fixation. The porous coatings are manufactured from either CP titanium or titanium alloy. Some acetabular components have screw holes located on the outer shells to allow for adjunctive fixation with bone screws.

The metal/polyethylene acetabular components are two-piece modular components consisting of 28mm inner diameter ultrahigh molecular weight polyethylene (UHMWPe) bearing insert liners fitted to the outer shells by means of snap-fit locking mechanisms. The metal outer shells were manufactured from either commercially pure (CP) titanium or titanium alloy (Ti-6Al-4V). The outer surfaces of the acetabular components all have either sintered or plasma sprayed porous coatings to provide for biological ingrowth as a means for primary fixation. The porous coatings are manufactured from either CP titanium or titanium alloy. The acetabular components have screw holes located on the outer shells to allow for adjunctive fixation with bone screws.

The femoral prostheses components for both the investigational and control device configurations are manufactured from either titanium or cobalt chrome alloys. The femoral components have proximal tapers to receive the modular ball heads having diameters that match the inner diameters of the acetabular prostheses. Both cemented and uncemented femoral prostheses were implanted in these studies.

Survival Curves for Metal-on-Metal Implants from Three Manufacturers

Introduction

In the September 4, 1987 Federal Register, FDA issued a final rule classifying hip joint metal/metal semiconstrained prosthesis with a cemented acetabular component (888.3320) and the hip joint metal/metal semiconstrained prosthesis with an uncemented acetabular component (888.330) into Class III. On September 25, 2000, the Orthopedic Surgical Manufacturers Association (OSMA) submitted a petition under section 513 (b) (2)(A) of the Act requesting a change in the regulatory classification for these devices from Class III to Class II. The reclassification petition was reviewed at an Orthopaedic and Rehabilitation Devices Panel meeting on August 8, 2001. At that meeting, the panel voted to recommend against reclassification and cited the reasons for their recommendation. The FDA concurred with the panel, and in the Federal Register published on September 6, 2002, denied the request for reclassification and specified the reasons for this decision.

Subsequent to the decision by FDA to deny the OSMA petition, OSMA held meetings with the agency to discuss where the original petition was deficient and how these deficiencies might be addressed in a second reclassification petition. One of the deficiencies to be addressed was the lack of longer-term, i.e., 4-7 years follow-up information on the performance of the metal-on-metal hips from the studies presented in the original petition. At a meeting held at the agency on January 23, 2002 and during teleconferences held on April 25 and September 4, 2002, FDA advised the OSMA members to present a device survivorship analysis of the metal-on-metal hip devices from the clinical studies described in the original petition as a means for providing this information. The OSMA member companies agreed to this recommendation.

The following provides a comprehensive report of the device survivorship from four clinical investigations of metal-on-metal total hip prostheses sponsored by three OSMA member companies. Two of the studies, of considerably longer duration, sponsored by Zimmer (formerly Centerpulse), were not part of the original reclassification petition and are now included. (These data were added to address the concerns by FDA and the panel about the lack of longer-term data.) The other two studies, from Biomet and DePuy, were part of the original petition. All of the metal-on-metal hip devices from these studies were subsequently cleared for commercial distribution by FDA.

Materials and Methods

Data from subjects enrolled in four FDA approved Investigational Device Exemption (IDE) clinical investigations approved between May 1995 and December 1999 were used to determine the device survivorship of metal-on-metal total hip replacement prostheses. A total of 44 clinical investigators participated in the IDE studies. Information regarding the status of the metal-on-metal hip prostheses was

developed by two means: 1) the sponsors of the IDE studies supplied OSMA with the most recent data compiled from the clinical evaluations of the study subjects, and 2) subjects who were unwilling or unable to return for follow-up evaluations were contacted by the participating IDE clinical investigators and asked to complete a questionnaire to determine the status of their hip replacement. Information from the investigational device treatment groups only, i.e., those with metal-on-metal hips, and not the control device treatment groups, were used for this report.

Pooling of the data was justified based on the similarities in the materials used to manufacture these devices and on the design specifications of metal-on-metal articulations. A total of 1335 hips were enrolled in four IDE clinical investigations. Of these, there were 678 metal-on-metal hips implanted in 632 subjects (46 bilateral cases) that were made available to OSMA for analysis. The date from the most recent evaluation/questionnaire was used to determine the time point for survivorship of the hip replacement and subjects were considered as having their hip replacement prostheses in place up to the point at which they were censored. For this analysis, failure is defined as the removal of one or more of the device components for any reason. Device survivorship results were calculated and presented according to the Kaplan Meier method[1]. Discrete intervals are not used in this method; survival and confidence intervals are recalculated each time a failure is observed. A survival estimate is calculated up to the time when there are 20 evaluable hips remaining that have not yet failed or been lost to follow-up, in accordance with the recommendation of Dorey and Amstutz[2].

Results

Excellent survival results are associated with metal-on-metal total hips. The survival curves reported here characterize survival in 678 metal-on-metal total hips implanted between September 1995 and August 2000. Company A contributed 97 cases, Company B 273, and Company C 308. Mean age at surgery was 57 years (± 13, range 18 to 90). All were implanted in four randomized IDE studies. Mean weight was 189 lbs (± 43, range 95 to 396); mean height was 68 inches (± 4, range 52 to 82). Gender distribution was 276 female (41%), 402 male (59%). A primary diagnosis of osteoarthritis was recorded in 506 hips (75%). Mean follow-up was 4.1 years (± 2, range 0 to 8). There were 26 deaths reported, none attributed to the implant.

There were ten failures where failure was defined as the surgical removal of one or more components for any reason. The average time to failure was 2.8 years (± 2.06, range 0 to 6.2). One of the failures included was actually the result of an intra-operative error. This hip was revised immediately postoperative, just after the patient had been brought to the recovery room. It was found that an incorrect head had been installed. The reason for failure in the remaining nine implants was trauma in 3, impingement in 1, dislocation in 3, and 2 were revised for aseptic Acetabular loosening.

The failures that were definitely attributed to trauma by the investigator included (1) a fall, (2) a hip that loosened when the patient used the operative hip to move a washing machine and (3) trauma that resulted in chronic dislocation. The revision due to impingement probably reflects an error in implant positioning. The three failures associated with dislocation most likely reflect technical issues associated with soft tissue

balancing or implant positioning. Finally, there were two implants revised for acetabular loosening. In one of these two instances, the investigator suspected the cause to be a fall suffered some months previously, while roller-blading, and felt that the failure might have been avoided if screws had been used. The remaining patient revised for acetabular loosening had extensive joint disease. This patient received a second THA on the contralateral hip, and a total shoulder arthroplasty, prior to loosening of the study acetabulum.

This mutli-center, multi-manufacturer group of metal-on-metal THA patients had 10 failures in 678 hips (1.5%). Excluding the intra-operative error where an incorrect head was installed, the failure rate was 1.3%. All of the failures reported fall into expected failure categories, and there was no instance where a failure was attributed by the investigator to the metal-on-metal articulation: it may be noteworthy that there was not a single deep infection reported. Accordingly, these results provide evidence that MOM articulation failure modes are equivalent in type and proportion to failures observed in metal-on-poly, ceramic-on-poly, and ceramic-on-ceramic articulation THA.

Figure 1 shows the survival curve for all metal-on-metal implants, pooled across studies. Here, the Kaplan-Meier survival estimate is 98.1% at 5 years postoperative and 97.0% at 7.3 years. Figure 2 shows the survival curve when data collected by a survey is included. The survey data came from Company A, and was conducted by mail. It did not include a physical examination of the patient. Where survey data are included, the Kaplan-Meier survival estimate is 98.2% at 5 years postoperative and 97.4% at 7.6 years. After 7.6 years, there were 19 hips with follow-up information ranging from 7.7 to a maximum of 8.5 years, with no reports of failure in any of these hips. Figure 3 shows survival for metal-on-metal hips broken down by manufacturer. The Kaplan-Meier survival estimate for Company A is 100% at 5.0 years postoperative. For Company B, the survival estimate is 99.4% at 5.0 and 7.0 years postoperative; and for Company C, the survival estimate is 96.6% at 5.0 and 7.1 years postoperative.

These results provide evidence that metal-on-metal articulation provides durable and equivalent survival results, regardless of manufacturer.

Discussion

The National Institute for Clinical Excellence (NICE, UK) "...considers it reasonable to recommend consideration of prostheses with a minimum of 3 years revision rate experience [from multi-center randomized trials] if their performance is consistent with the benchmark of a 10% revision rate at 10 years." [3] This standard has been exceeded in the results presented here with respect to length of follow-up by a factor of 2.5. A 7.6-year survival estimate of 97.4% is entirely consistent with a ten-year revision rate that is substantially less than 10%. Moreover, the survival estimates achieved individually by different manufacturers, with different metal-on-metal implants, are consistent with a ten-year revision rate of less than 10% in each instance.

Accordingly, concerns regarding the survival rate of present generation metal-on-metal stemmed hip prostheses have been addressed adequately by these results. A decision to down-classify metal-on-metal hips from Class III to Class II is warranted.

Figure 1

Kaplan-Meier Survival Estimates (95% C.I.)
Data Pooled Across Manufacturers

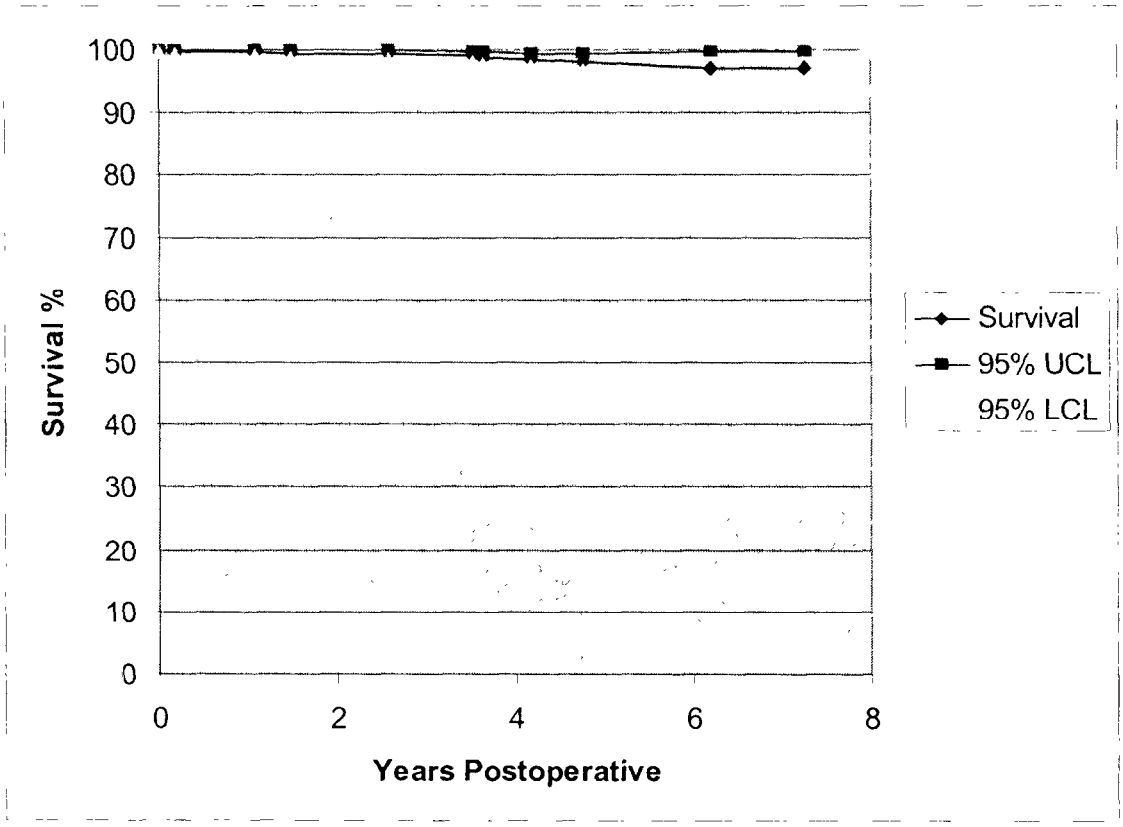


Figure 2

Kaplan-Meier Survival Estimates (95% C.I.)
Data Pooled Across Manufacturers
Non-Clinical Survey Data Included

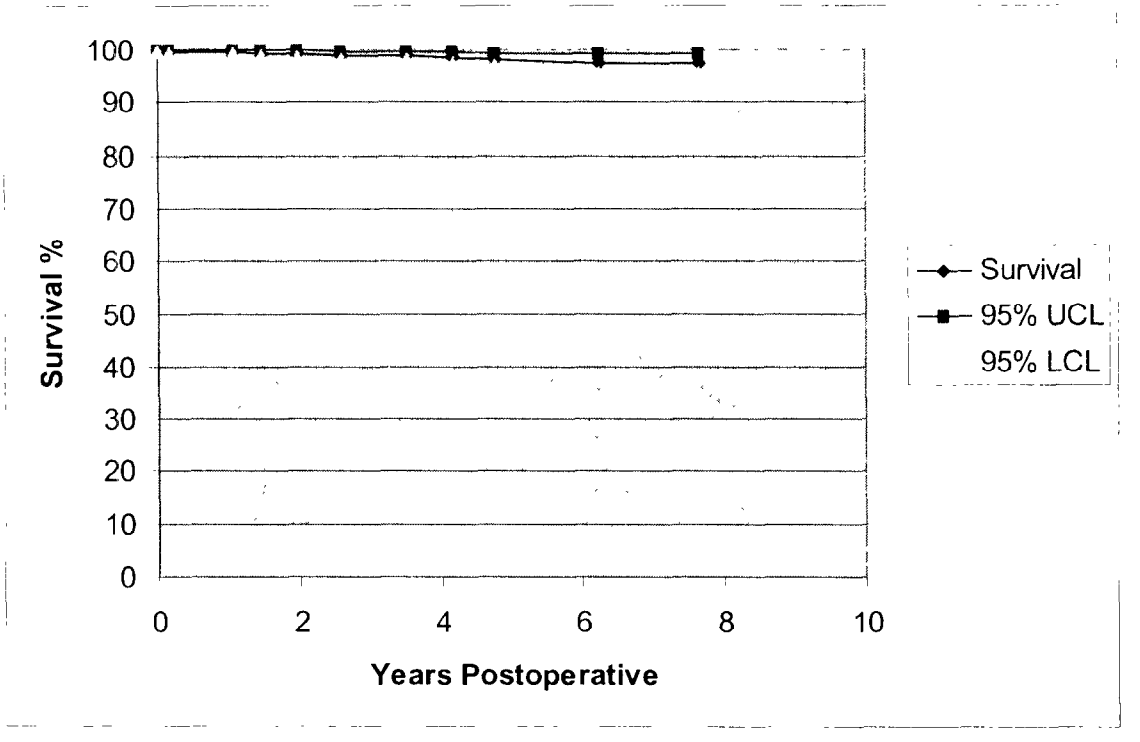
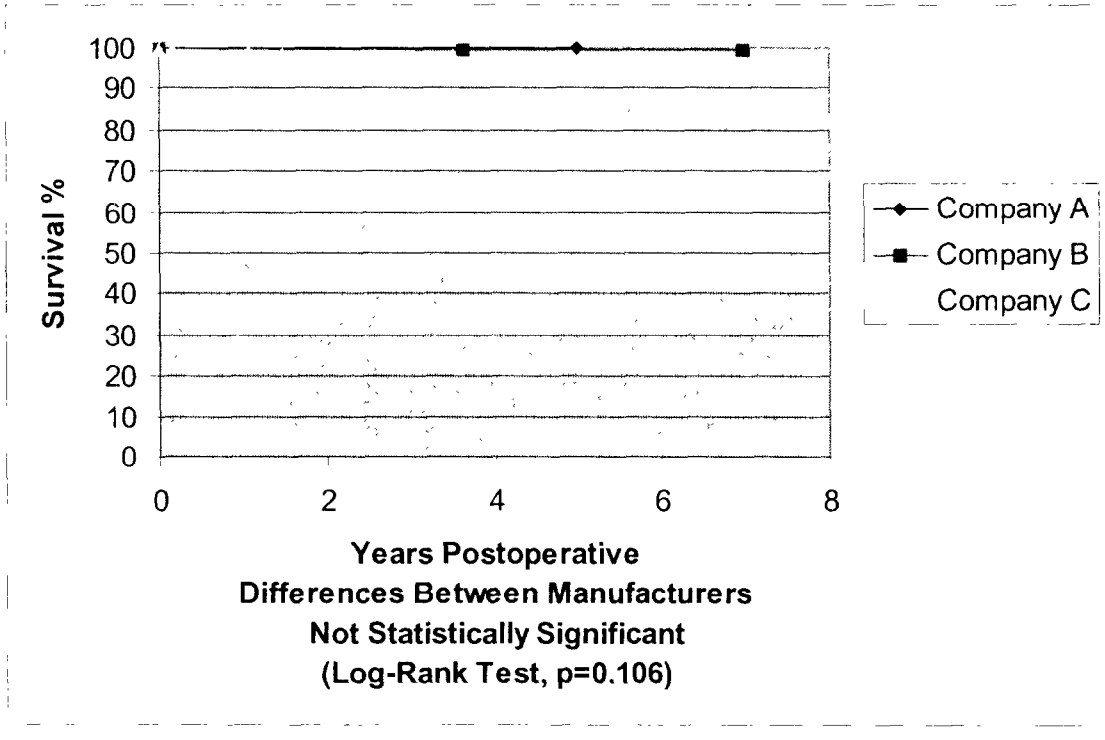


Figure 3

Kaplan-Meier Survival Estimates
Survey Data not Included



[1]Kaplan EL, Meier, P: Nonparametric estimation from incomplete observations. J AM Stat Assoc 53:457, 1958.

[2]Dorey, F, Amstutz, HC: Survivorship Analysis in the evaluation of joint replacement. The Journal of Arthroplasty Vol. 1 No. 1 pp 63-69, March 1986.

[3]Guidance on The Selection of Prostheses for Primary Total Hip Replacement. National Institute for Clinical Excellence (UK), April 2000.
www.nice.org.uk/pdf/Guidance_on_the_selection_of_hip_prostheses.pdf

B. Published Clinical Studies

The following is a summation of several significant articles found in published literature using a search of various medical databases.

Albrecht-Olsen P, Owen-Falkenberg T, Burgaard P, Andersen PB. Nine-year follow-up of the cementless ring hip. Acta Orthop Scand 1989 Feb;60(1):77-80.

Reviewed 238 Ring prostheses implanted during the period 1968-1979. Of those cases, 127 with a median follow-up of 9 years were available for evaluation with 90% of those patients demonstrating excellent/good results upon self assessment. Using the Charnley scale, 87% had a pain score of 4 or greater (score of 6 = no pain), 76% had a motion score of 4 or greater, and 57% had a walking score of 4 or greater. The author cites an infection rate of 2.5% (6 deep infections, 16 superficial infections). Four dislocations were also encountered. At the time of this evaluation, 17% (n=40) of the patients had been revised, mainly due to pain. Overall results predicted an 81% survival rate at 12 years, comparable to outcomes seen with metal-on-polyethylene articulation

Almby B, Hierton T. Total hip replacement: a ten-year follow-up of an early series. Acta Orthop Scand 1982 Jun;53(3):397-406.

Reported on 93 patients receiving the Muller device, 57% of which had been followed for more than 10 years. Using the Charnley scale (6 possible points in each category), 90% had pain rating of 4 or better or a range of motion greater than 100°. Nine deep infections were reported. Thirty patients died (26 unrelated to device, 1 embolus, 1 ileus, 1 renal failure, 1 septic). Twenty-nine patients were revised (19 aseptically loose, 7 septically loose, 4 stem fractures, 1 fracture). Twenty-three acetabular and 16 femoral components showed signs of loosening. Femoral loosening was secondary to calcar resorption and cement settling in most cases. Survivorship in this series was calculated to be approximately 80% at 5 years and 57% at 10 years.

Andrew TA, Berridge D, Thomas A, Duke RN. Long-term review of ring total hip Arthroplasty. Clin Orthop 1985 Dec;(201):111-22.

Presented his results of 116 Ring patients followed for 8 years. Using the Harris scoring system (100 points possible), 33% of the patients had 80 points or greater with another 13% exhibiting total scores of 70-80. Using the Ring evaluation, 49% of the patients rated excellent or good. Two deep infections and 4 dislocations were encountered. Other complications included grade IV heterotopic ossification (5), fracture (4), embolic event (7), and sciatic palsy (1).

August AC, Aldam CH, Pynsent PB. The McKee-Farrar hip arthroplasty. A long-term study. J Bone Joint Surg Br 1986 Aug;68(4):520-7.
Results of 175 patients with the McKee-Farrar device at an average 13.9 years of follow-up are presented by August[4]. Using the Harris evaluation, the average total score was 76.4,

with 48.9% having excellent/good outcomes. On self assessment, 90% of the patients rated themselves as having a satisfactory outcome. Sixty-four patients were revised, mainly for loosening, stem fracture and bone fracture. Over 50% of the stems and cups showed signs of looseness radiographically. Additionally, the cup showed signs of protrusion in 62.5% of rheumatoid patients. Heterotopic ossification (grade IV) was reported in 2.7% of the cases. August calculated survival at 84.3% at 14 years and 27.5% at 20 years.

Djerf K, Wahlstrom O. Total hip replacement comparison between the McKee-Farrar and Charney prostheses in a 5-year follow-up study. Arch Orthop Trauma Surg 1986;105(3):158-62.

Presents results on 107 McKee-Farrar and 70 Charnley devices with 5 years followup. Analysis revealed 94% of patients to have no pain and 78% to have improved flexion. Unrelated death occurred in 12% of the patients. Six infections (3.4%) and 4 dislocations (2.3%) were reported. Other complications included trochanteric problems (2.8%), nerve injury (1.7%), deep venous thrombosis (1.7%), pulmonary embolus (0.6%), fracture (0.6%), and ossification (0.6%). Loosening was evident in 32% of the cases. Analyses showed no significant difference in the outcomes of either implant.

Jacobsson SA, Djerf K, Wahlstrom O. Twenty-year results of McKee-Farrar versus Charnley prosthesis. Clin Orthop Relat Res 1996 Aug;(329 Suppl):S60-8.

A comparison was performed by Jacobsson on a series of McKee-Farrar metal-on-metal patients and a series of Charnley metal-on-polyethylene patients. No major differences were observed between the two groups with regard to radiographs, Harris Hip Scores or walking ability. At 12 years, average Harris hip scores for the McKee-Farrar and Charnley were 82 and 83, respectively. At 20 years, average Harris hip scores were 75 and 77. Sixteen McKee-Farrar and eight Charnley devices were removed. No debris was noted in the McKee-Farrar retrievals. The infection rate is 2.8% for McKee-Farrar and 4.3% for the Charnley. The dislocation rate is 2.8% for the McKee-Farrar and 1.4% for the Charnley. Loosening of the McKee-Farrar was noted in 5 cups and 6 stems; 4 cups and 4 stems were loose in patients receiving the Charnley device. Extensive scalloping was observed in 5/11 Charnley devices. Nerve damage (1.9%) and femoral fracture (0.9%) were also reported with the McKee-Farrar device. Trochanteric pain (7.1%), deep venous thrombosis (4.3%), nerve damage (1.5%), pulmonary embolus (1.4%) and ectopic bone (1.4%) were experienced in the Charnley patients. This study determined that there was no statistically significant difference in survivorship at more than 11 years: 82% for the McKee-Farrar patients compared to 89% for the Charnley patients.

Jantsch S, Schwagerl W, Zenz P, Semlitsch M, Fertschak W. Long-term results after implantation of the McKee-Farrar total hip prostheses. Arch Orthop Trauma Surg 1991;110(5):230-7.

Analyzed followup at 14 years in a series of 248 patients with 330 McKee-Farrar devices. Only 56% of the patients were followed clinically to this period (24% died, 17% untraceable, 3% refused participation). Using the Mayo rating system, 48% of the patients

were found to have excellent/good ratings (62% if revisions are excluded). Based on radiographs available, 34% of the cups and 26% of the stems were unstable. There were 36 retrievals (22 cup and stem, 7 cup, 7 stem).

McKee GK, Chen SC. The statistics of the McKee-Farrar method of total hip replacement. Clin Orthop Relat Res 1973 Sep;95:26-33.

Reports on four series of patients treated with the various iterations of the McKee-Farrar device from 1956-1971. As shown in the attached tables, postoperative outcome improved through each design iteration, with approximately 89% achieving excellent or good outcomes in the 1965-69 series (4-7 year followup) and 97% achieving excellent or good outcomes in the 1971 series (2 year or less followup). Retrievals have occurred in 4% of the 1965-69 series and 0% of the 1971 series. Fifteen (15) deaths were reported in the 1965-69 series; two were reported in the 1971 series. The reported rate of infection was 4% in the 1965 series and 0% in the 1971 series. Two dislocations (2%) were also reported in each of these series. Other complications include pulmonary embolus, deep venous thrombosis, shaft perforation, hematoma and heterotopic ossification.

Ring PA. Five to fourteen year interim results of uncemented total hip arthroplasty. Clin Orthop Relat Res 1978 Nov-Dec;(137):87-95.

Presents results on 106 metal-metal Ring prostheses with 7-17 years followup. Postoperatively, 83% were assessed as excellent/good clinically. Outcomes of the various design iterations is again presented in this article. Thirteen retrievals have occurred (7 femoral failures, 2 pelvic failures, 3 combination failures, 1 ankylosis). Survivorship of patients implanted from 1968-73 was 81% at 18 years; survivorship was 95% at 16 years for those implanted from 1972-79.

Schmalzried TP, Szuszczewicz ES, Akizuki KH, Petersen TD, Amstutz HC. Factors correlating with long term survival of McKee-Farrar total hip prostheses. Clin Orthop Relat Res 1996 Aug;(329 Suppl):S48-59.

Thirteen McKee-Farrar patients (15 devices) with an average follow-up of 23.7 years are presented. The average Harris hip score of these patients was 86 with 11 patients having an excellent/good rating. These patients outscored a matched metal-on-poly control population on the SF36 Health Status questionnaire. Activity levels were also reported to exceed the averages for this age population. The only complication reported is that of lysis in three femurs and one acetabulum.

Zaoussis AL, Patikas AF. Experience with total hip Arthroplasty in Greece, the first 20 years. A particular reference to long-term results with the McKee-Farrar technique. Clin Orthop Relat Res 1989 Sep;(246):39-47.

Presents results on 38 McKee Farrar patients followed for 12-20 years, with 26 having greater than 15 years followup. At the time of this evaluation, 45% were found to have

very good outcomes. Fifty-three percent (53%) of the patients were pain free and 79% had 60-90° range of motion. Three infected components and four loose components were retrieved. There have been five dislocations (all in one patient). Nine components show looseness. Other complications include five peroneal nerve palsies, one cortical perforation and one ossification.

Lombardi AV Jr, Mallory TH, Ranaway CS, Williams J, Wixson R, Hartman JF, Capps SG, Kefauver CA. Short-term results of the M^2 a-taper metal-on-metal articulation. J Arthroplasty 2001 Dec;16(8 Suppl 1):122-8.

A polyethylene-free metal-on-metal acetabular system was designed in an effort to improve total hip arthroplasty (THA) longevity. Minimum 2- year follow-up results involving 72 polyethylene (PE) liner THAs and 78 metal liner THAs from a multicenter, randomized, controlled, investigational device exemption study was reported. Mean Harris hip scores of 95.54 (PE liner group) and 95.23 (metal liner group) were reported at mean follow-up intervals of 3.29 and 3.23 years. Radiographic evaluation revealed no evidence of early failure. No acetabular components were revised or were pending revision. No statistically significant differences in the data were calculated between liner types except for the immediate postoperative (P=.0415) and minimum 2-year follow-up (P=.0341) angles of inclination. The M^2 a-taper metal-on-metal articulation may represent a viable alternative for THA in younger, higher demand patients.

Dorr LD, Wan Z, Longjohn DB, Dubois B, Murken R. Total hip arthroplasty with use of the Metasul metal-on-metal articulation. J Bone Joint Surg Am 2000 Jun;82(6):789-98.

Between 1991 and 1994, seventy patients had a total hip replacement with the Metasul metal-on-metal articulation and a cemented Weber cup. Fifty six patients had complete clinical and radiographic data four to 6.8 years after the operation. There was one mechanical failure (2 percent). Thirty six of 47 patients who completed the patient self assessment form rated their result as excellent; seven, as very good; two, as good; one, as fair; and one, as poor. Wear could not be measured on radiographs because of the metal-on-metal articulation. No hip had radiographic evidence of acetabular osteolysis and two hips had calcar resorption, but there was no other evidence of focal osteolysis. From their four to seven year experience with the device the authors feel that the clinical results are similar to those of total hip replacements with a metal-on-polyethylene articulation. They believe the device may have a role in reducing the wear that occurs with total hip replacement and that the device appears particularly indicated for younger patients.

MacDonald SJ, McCalden RW, Chess DG, Bourne RB, Rorabeck CH, Cleland D, Leung F. Metal-on-metal versus polyethylene in hip arthroplasty: a randomized clinical trial. Clin Orthop Relat Res 2003 Jan;(406):282-96.

A prospective, randomized blinded clinical trial was done to evaluate polyethylene versus metal bearing surfaces in total hip replacement. Forty one patients were randomized to receive either a metal (23 patients) or a polyethylene (18 patients) insert. The femoral and acetabular components were identical with the acetabular insert the only variable.

Patients were assessed preoperatively and postoperatively using radiographs, multiple outcome measures (Western Ontario MacMaster University Score, Harris hip score, Short Form-12), erythrocyte metal ion analysis (cobalt, chromium, titanium). Patients were followed up for a minimum of two years (mean 3.2 years; range, 2.2-3.9 years). There were no differences in radiographic outcomes or outcome measurement tools between patients. Patients receiving a metal-on-metal articulation had significantly elevated erythrocyte and urine metal ions compared to patients receiving a polyethylene insert. Patients who had metal-on-metal inserts had on average a 7.9 fold increase in erythrocyte cobalt, a 2.3 fold increase in erythrocyte chromium, a 1.7 fold increase in erythrocyte titanium, a 35.1 fold increase in urine cobalt, a 17.4 fold increase in urine chromium, and a 2.6 fold increase in urine titanium at 2 years follow-up. Patients receiving a polyethylene insert had no change in erythrocyte titanium, urine cobalt or urine chromium and a 1.5 fold increase in erythrocyte cobalt, a 2.2 fold increase in erythrocyte chromium, and a 4.2 fold increase in urine titanium. Forty-one percent of patients receiving metal-on-metal articulations had increasing metal ion levels at the latest follow-up. The clinical significance of this remains unknown. Only through thorough long-term clinical analysis will appropriate conclusions be valid. Metal-on-metal total hip replacements perform well clinically; however, only with time will the risk to benefit ratio become clear.

Lhotka C, Szekeres T, Steffan I, Zhuber K, Zweymuller K. Four-year study of cobalt and chromium blood levels in patients managed with two different metal-on-metal total hip replacements. J Orthop Res 2003 Mar;21(2):189-95.

In 259 patients with total hip replacement, blood cobalt and chromium concentrations were measured with atomic absorption spectrophotometry over a period of four years after arthroplasty. Of the patients enrolled in the study, 131 had been managed with a METASUL cobalt-chromium alloy metal-on-metal bearing combination, while 128 had been given a SIKO-MET-SM21 cobalt-chromium alloy metal-on-metal combination. The control group consisted of 31 age- and gender-matched subjects. Compared with the controls, all of the patients had higher cobalt and chromium levels. Cobalt concentrations were up to 50 times higher, while chromium concentrations were up to 100 times higher. Both systems showed evidence, in the whole-blood samples, of wear debris production by the implants. Therefore, patients managed with metal-on-metal bearing combinations should be carefully monitored in order to ensure that any local or systemic complications are detected early on. According to the authors, the cause and effect relationship between metal wear debris and local or systemic disease has not been conclusively proved, although complications from metal wear products are a subject of concern. Any metal-on-metal bearing combination used in joint replacements must, therefore, be designed and manufactured in such a way as to produce minimal debris.

Lombardi AV Jr, Mallory TH, Cuckler JM, Williams J, Berend KR, Smith TM. Mid-term results of a polyethylene-free metal-on-metal articulation. J Arthroplasty 2004 Oct;19(7 Suppl 2):42-7.

One hundred ninety-three patients (195 hips) were enrolled into this prospective, randomized, controlled multi-center investigational device exemption study. Ninety eight patients (99 hips) with 46 polyethylene liners and 53 metal liners had minimum 5-year followup (mean 5.7 years). Average followup , Harris hip score improvement, and radiographic analysis were not statistically different between groups. No stress shielding or osteolysis was observed in either group. Three polyethylene liners and no metal liners had acetabular radiolucencies >1 mm in 1 or more zones. There were no device related complications, no acetabular revisions performed, and none pending in either group. Based on these mid-term results, the authors conclude that a metal-on-metal articulation represents a viable alternative in young, high-demand, active patients. The device used was a M^2 a Taper Metal-on-Metal Articulation (Biomet Orthopaedics, Warsaw, IN).

Jacobs M, Gorab R, Mattingly D, Trick L, Southworth C. Three- to six-year results with the Ultima metal-on-metal hip articulation for primary total hip arthroplasty. J Arthroplasty 2004 Oct;19(7 Suppl 2):48-53.

One hundred seventy-one primary total hip arthroplasties were evaluated in a prospective, randomized study. Ninety-five involved a metal-backed cup with an all-metal liner and 76 involved a metal backed polyethylene cup that was used as the control. All were implanted with an S-ROM cementless femoral component with a 28-mm head. The mean followup period was 3.7 years (range 3.0-5.7). The average postoperative Harris hip score was 95.4 (range 65-100) for the metal-on-metal group and 96.1 (range 65-100) for the metal- on- polyethylene group. Radiographic results were not statistically different between the two groups. Early results show metal-on-metal articulation has been successful to date and justify continued clinical use.

Long WT, Dorr LD, Gendelman V. An American experience with metal-on-metal total hip arthroplasties—a seven year follow-up study. J Arthroplasty 2004 Dec;19(8 Suppl 3):29-34.

This study reviews the clinical performance of 161 hip arthroplasties (154 patients) with the Metasul metal-on-metal articulation and an uncemented modular acetabular component. Between 1995 and 2002 clinical evaluation and radiographic follow-up of patients included Harris hip scores, patient self-assessment, and radiographs. Twelve operative site complications (7.5%) included 6 revision operations (3.7%) and 3 other complications (1.9 %) not needing reoperation. Six revision operations (3.7%) included 1 femoral revision for aseptic loosening (0.06%) and 5 acetabular revisions (3.1%). One cup revision was for recurrent dislocation, 1 for disassociation of the acetabular insert from the cup, 1 for infection, and 2 for unexplained pain. Histologic evidence did not support the diagnosis of metal hypersensitivity in either case of unexplained pain, and 1 had relief following spine surgery. A focal radiolucency, identified as calcar resorption, was observed in 9 patients. Metal ion levels were not tested in patients as part of these studies. The authors note that after 40 years of use, there is no evidence that metal-on metal articulations have been a cause of cancer. The strength of this study is that it confirms that the high incidence of early aseptic loosening has been improved with this modern metal-on-metal articular system.

Delaunay CP. Metal-on-metal bearings in cementless primary total hip arthroplasty. J Arthroplasty 2004 Dec;19(8 Suppl 3):35-40.

One hundred cementless titanium primary total hip arthroplasties with 28 mm Metasul bearings were prospectively studied (osteoarthritis in 76% of hips, mean age 59.6 years). Ninety-eight were reviewed after a 6-year average follow-up (range, 17-126 months) with clinical results graded excellent and good in 97%. One femoral component was revised for aseptic loosening at 7.8 years. Postoperative cobalt level was higher than the upper "normal" value (5µg/L in whole blood) for 16 cases. No significant relationship could be established between cobalt concentration increase and any demographic or surgical data, including activity level, except anteversion of the cup >25°. In this early experience, impingement due to a head sleeve has been the main cause of dislocation and failure, and systemic cobalt survey appeared to be a good indicator of metal-on-metal bearing mechanical behavior. According to the author, the absence of detectable wear and, above all, the lack of relationships among increased cobalt level, age and high patient activity are encouraging findings for continued use of metal-on-metal bearings in young and/or active patients.

Migaud H, Jobin A, Chantelot C, Giraud F, Laffargue P, Duquennoy A. Cementless metal-on-metal hip arthroplasty in patients less than 50 years of age: comparison with a matched control group using ceramic-on-polyethylene after a minimum 5-year follow-up. J Arthroplasty 2004 Dec;19(8 Suppl 3):23-8.

Thirty nine cementless hip arthroplasties using metal-on-metal articulation (Metasul) were consecutively implanted in 30 patients less than 50 years of age and compared to a matched control group (by age, diagnosis, Devane activity, and Harris hip scores) of cementless arthroplasties using ceramic-on polyethylene articulation. The Harris hip score at follow-up (minimum 5 years) for the metal-on-metal was 94.9 (range 74-100). After the same follow-up, the results with the ceramic-on-polyethylene were significantly worse; 9 osteolyses and 7 surgical revisions related to wear (none in the metal-on-metal). Five year survival rates were 97% ±2% for the ceramic-on-polyethylene and 100 % for the metal-on-metal. The metal-on-metal may be recommended to prevent wear problems in younger and more active patients; however, a longer follow-up is required to confirm this encouraging data.

Dorr LD, Long WT, Sirianni L, Campana M, Wan Z. The argument for the use of Metasul as an articulation surface in total hip replacement. Clin Orthop Relat Res 2004 Dec;(429):80-5.

Metasul metal-on-metal articulations have been used for 15 years in approximately 300,000 total hip replacements. The authors have used Metasul articulations in three clinical studies and have shown clinical success as measured by Harris Hip Scores and patient self-assessment. The authors have noted the usual mechanical complications. The only complications have been mechanical, including two-cup loosenings and 24 dislocations in a total of 582 patients (619 hips; 3.8%) who had Metasul articulations and

were included in these studies. In the randomized study, the group who had Metasul articulations had no clinical results or complications different from the control ceramic-on-polyethylene group. Authors of retrieval results in the literature report low annual linear wear rates and no consequences of elevated Co ion levels. Currently, the scientific evidence of the results using the Metasul articulation would recommend its continued use in any patient who does not have compromised renal function.

The review of the published literature suggests that good long-term results comparable to current metal-on-polyethylene prostheses can be achieved with well-designed metal-on-metal devices. As outlined, the complications encountered with metal-on-metal devices are common to current total hip arthroplasty. This review further highlights the importance of preventive therapies and proper surgical technique in good clinical outcomes.

Published reports by Dorr, et al. (1996), (2000), (2004), Hilton, et al. (1996), Wagner and Wagner (1996) and Weber (1996) of the clinical experience with the Metasul® (Sulzer Orthopedics, Austin, TX) metal/metal semi-constrained hip designs lend further support to the conclusions drawn from the results reported here. Copies of these reference articles are provided in Appendix 3.

C. Published Biological Studies

Short and Long-Term Biological Effects Of Metal-On-Metal Total Hip Replacement From Human Retrieval Studies and In Vitro Studies

Information from studies of long-term hip replacements at revision or autopsy

The clinical history of metal-on-metal implants is more than 3 decades long. The study of tissues from long-term McKee-Farrar metal-on-metal implants can provide an insight into the anticipated long-term tissue effects of contemporary metal-on-metal total hip replacements. Zahiri et al [47] reported on a small group of 15 patients with well-functioning McKee-Farrar total hip replacements between 21 and 26 years post-operatively and compared the clinical and radiographic characteristics to a similar group that had been revised from 6 months to 21 years. They found that unfavorable biomechanics including reduced offset and varus positioning could result in increased joint reaction forces that could contribute to loosening. Metal wear from the bearings was not a cause of failure and although radiographic osteolysis occurred in 6 of the 15 revised hips and 2 of the surviving hips, histological examination of the revision tissues showed only minimal to moderate numbers of macrophages with metal, minimal chronic inflammation, but small to high numbers of giant cells associated with cement debris. In another group of long-term McKee-Farrar retrievals after an average of 21 years, the tissues from 5 loose implants were characterized by extensive fibrosis and a foreign body inflammatory infiltrate of macrophages, some of which contained metal, and/or brown hemosiderin pigment, and giant cells that were associated with cement debris. [37]

In both of the above examples, the tissue response to bone cement appeared to predominate over the response to metal from the implant. This is consistent with the generally low amount of wear as reflected in the lack of visible metal staining of the tissues. For example,

from an original group of 248 patients implanted at one center with McKee-Farrar total hips, only one out of 36 revisions at an average of 8 years had metallosis. [29] Szuszczewicz et al [39] reported that, despite progressive pelvic osteolysis seen radiographically in a patient with a McKee-Farrar that was revised after 13.5 years for socket loosening, there was no metallosis and only minimal macrophage reaction within the tissues which were described as grossly hemorrhagic, tan-colored and ranged from rubbery to friable in texture. Histologically, they contained organized fibrous tissue that was partly necrotic, and contained fat cells, hemorrhage, scattered macrophages and rare giant cells. Focal dark areas contained both metal and hemosiderin deposits and the cytoplasm of phagocytes contained small granular particles and round to oval clear spaces consistent with PMMA and barium sulfate. Metallosis was similarly absent from 9 revised McKee-Farrar implants from a group of 52 hips evaluated between 12 and 20 years despite the mechanical loosening or dislocations in most of these revisions. [48]

A thorough histopathological examination of tissues from a long-term McKee-Farrar implant was performed following the donation of the body to a willed joint program. [8] Samples from periprosthetic capsule, interface membrane, kidney, lymph nodes, spleen and liver were examined for the amount and type of wear debris and any associated tissue pathology. Despite 30 years of use, and the loosening of the cemented femoral stem, the tissues around the implant showed only a small amount of metal staining around the loose stem. Histologically there was a moderate histiocytic response but giant cells and large tissue spaces suggested that bone cement, rather than metallic particles, were the predominant wear particles. Cobalt and/or chromium-based particles large enough to be visible at the light microscope level were essentially absent from the reticulo-endothelial tissues although particles of environmental origin were present. Using energy-dispersive x-ray analysis (EDAX), none of the particles in any of the organ tissues

were identified as cobalt-chromium alloy except for one particle in a phagocytic cell within the liver. Lymphocytes and plasma cells were rare and polymorphonuclear leukocytes were absent. No abnormalities were noted in any of the organ samples despite finding high levels of cobalt (average of 4 specimens was 119ng/g, control tissue 27ng/g) and chromium (ave 105 ng/g, control undetectable) ions in the liver. Presuming that the sampled tissues were representative of the particle burden of the organ as a whole, the absence of detectable particles suggested that either migration away from the joint was limited, or the particles that had migrated were too small to be detected using the methods employed, or they had already dissolved.

The metal particle migration from total hip replacements with metal-polyethylene bearings was studied in group of 30 autopsy retrievals collected after an average of 5.8 years (range 3.6 to 14.3 years) from patients ranging in age from 43 to 91 years. [41] Light and electron microscopy and identification of particle species with x-ray microanalysis demonstrated sub-micrometer metal particles within macrophages in the liver and/or the spleen in 11 of 15 patients with a revised arthroplasty and in 2 of 15 patients with primary hip replacement. In the patients with a revised hip replacement, the particles were present in the spleen alone in 5 patients, in both the liver and spleen in another 4 patients, and in the liver alone in 2. Based on the elemental identification of the particles, it was shown that the particles had been generated from the non-bearing surfaces including loosened components, ancillary fixation wires, plates or screws, and a well-fixed acetabular component and its fixation screws. In the patients with primary hip replacement, metal particles generated between non-bearing surfaces were detected in the liver of one patient and the spleen of another patient. The size of disseminated particles ranged from 0.1 up to 8 microns with most particles measuring less than 1 micron. The particles were phagocytosed by macrophages which formed focal aggregates in the organs without apparent

toxicity. In the spleen, macrophages containing metal particles were found primarily within the lymphatic sheaths surrounding arterial vessels where they formed foreign body granulomas. In the liver, the metal particles were found in focal clusters in macrophages of the portal tracts and distributed around venules in the parenchyma. These particles were commonly mixed with particles from environmental origins such as silicates, and particles containing titanium or aluminum.

In a separate report, Urban et al [40] described finding chromium particles in samples of kidney taken at autopsy from 2 patients with total joint replacements. One patient had well–functioning bilateral total knee implants with cobalt-chromium alloy on polyethylene bearings for 15 years. The second case had a history of multiple total hip replacement revisions over a period of 4 years prior to autopsy. At autopsy, the cobalt chromium alloy femoral implant in case 2 was noted to be loose and there had been impingement wear of the femoral head, and a stainless steel fixation plate was noted to be corroding. Minute particles identified as chromium by EDAX were present in tubular cells in both cases but without apparent pathologic significance. Interestingly, particles of the total joint alloy were not present in the kidneys although they were found in the lymph nodes, liver and spleen of these patients.

The increased numbers of particles in patients with mal-functioning implants has been previously reported. For example, in a post-mortem study, Case et al [10] compared the extent and effects of dissemination of wear debris in 13 patients with metal implants from 2 months to 14 years, with grossly variable degrees of wear and damage. Metal was found in local and distant lymph nodes, bone marrow, liver and spleen only in those cases with gross wear or damage. The amount of metal, as measured from inductively coupled mass spectroscopy of periprosthetic tissues, was highest in 4 cases with loose joint prostheses (2 stainless steel total hip replacements

7.5 and 8.5 years post-operatively, one cobalt chromium alloy Thompson hemiarthroplasty at nine years and a steel and titanium a total knee 14 years post-operatively). Histologically, there was a higher concentration of metal in the iliac lymph nodes closest to the joints and more metal was present in the cases that were loose. Particles were concentrated in sinus macrophages causing mild histiocytosis, but around the loose total knee, the accumulation of the metal-laden cells resulted in large numbers of non-caseating, epithelioid granulomas and extensive necrosis of much of the normal lymphoid tissue.

In the remaining cases with less wear, a subtle increase in fibrosis and scarring of the lymph nodes was reported. The presence of macrophages with metal was associated in all cases with a reduction in normal lymphoid tissue. Metal particles were found in the portal tract macrophages and in Kupffer cells of the liver in lower amounts than in the lymph nodes. In two cases, macrophages were found in the spleen within the sinuses and red pulp but there is no mention of any associated pathology. No implant generated particles were detected in the lung, and there were no detectable cellular changes associated with a small number of metal particles in the renal tubular epithelial cells. The implant related particles contained cobalt chromium and were described as needle-shaped from 10 to 70nm in diameter. At the transmission electron level, morphological changes within the nuclei of macrophages with ingested metal particles were seen. For example, the nucleus became rounder and paler, indicating a loss of heterochromatin, and in some cases, the nucleus was condensed, suggesting an apoptotic response. [28]

In summary, studies of tissues from loose and well-functioning, long-term metal-on-metal implants show that the metal debris is well tolerated. Osteolysis may occur in association with the added particle burden from bone cement or from unintended bearing surfaces in poorly

functioning implants. Metal particles migrate from the joint and can be detected in the form of particles and/or ions in organs, but with minimal pathological significance. The information gathered from these first generation implants should be relevant to the expected clinical performance of contemporary metal-on-metal implants.

Histological Findings In Mid-Term Contemporary Metal-On-Metal Total Joints.

In clinical reports of hips with second-generation metal-on-metal bearings, with mid-term follow-up, osteolysis is rare, as predicted from hip simulator studies and the clinical results of the long-term first-generation implants.[16,33,35] Beaulé et al, however, have reported a case of a well-fixed, cementless total hip replacement with a 28-mm Metasul metal-on-metal bearing (Zimmer, Winterthur, Switzerland) with progressive femoral osteolysis at 2 years post-operatively. [3] There was minimal bearing surface wear and only small numbers of inflammatory cells in the tissues suggesting that this was a case of osteolysis secondary to joint fluid pressure, rather than particle-induced osteolysis.

In a group of 98 cementless titanium primary total hip arthroplasties with 28-mm Metasul bearings studied prospectively up to 6-year average follow-up (range, 17-126 months) Delaunay [16] reported that one femoral component was revised at 7.8 years for aseptic loosening and osteolysis, thought to have been the result of additional wear from the impingement between the head sleeve and the socket that was noted intraoperatively. There was metallosis of the joint tissues and histological features consistent with an immune response, that is, lymphocytes and plasma cells were prominent.

A larger group of metal-on-metal implants with a clinical history of pain and /or osteolysis and with histological findings consistent with a metal sensitivity reaction was reported by Willert et al [45]. The characteristic histological features within the periprosthetic tissues of

this group of failures included diffuse and perivascular T and B lymphocytes and plasma cells, thickened vessels, massive fibrin deposits, infiltrates of eosinophilic granulocytes, and tissue necrosis. Only a few metal particles were detected but macrophages often contained inclusions of unidentified material. Willert had previously examined tissues from first-generation metal-on-metal implants and did not report these sensitivity-like reactions.[44,46] However, when he re-examined the tissue slides from a group of old McKee retrievals, he noted lymphocytes in cases that had been categorized as infected. He now suspects that some of these infected cases were actually showing signs of metal sensitivity and he concludes that metal sensitivity reactions were present in about half of the failed first-generation retrievals he examined, although to a lesser extent. [43]

Other reports of similar lymphocyte infiltrates around tissues from revised contemporary metal-on-metal components have been made but were usually accidental findings as the components were revised for other reasons. [2,6,17] Revisions for suspected metal sensitivity alone are rare [33,38] and none were associated with a dermal response. Interestingly, post-operative excematous reactions were reported in a group of 5 out of 92 patients receiving cobalt chromium alloy total knee implants, [36] but the relatively high numbers in this group and the rarity among even larger series of total knee recipients, including those with cobalt particulates in the tissues [30] leads one to question if the alloy, and not some other substance, was the cause.

In 1996 Merritt et al [34] reviewed the literature on metal sensitivity and concluded that the incidence was rare, probably less than 0.1%. While it is impossible to obtain an updated figure of the exact incidence of this problem, Prof. Han Willert, who is one of the foremost investigators in this field, agrees that the incidence is still very rare despite a huge increase in the number of patients receiving a metal-on-metal implant. [45] It would appear that the reported

cases probably represent a fraction of 1% of the approximately 350,000 second-generation metal-on-metal implants implanted to date.

Tissue necrosis has been reported around metal-on-metal joints both in the presence and absence of lymphocytes.[15,17,45] Generally the local inflammatory response and number of histiocytes is about one grade lower than that around metal-on-polyethylene joint tissues [17], possibly because the smaller metal particles do not elicit the same cellular response or because there are fewer particles in the local tissues and therefore fewer particles per cell. This is consistent with the lower incidence of periprosthetic osteolysis around metal-on-metal implants despite the fact that macrophages that phagocytose metal particles have been shown to produce inflammatory pro-osteolytic cytokines.[9,12,21] There are simply fewer cytokine-producing macrophages than required to produce osteolysis. Tissues from 2 well-functioning autopsy-retrieved Metasul implants were reported to contain minimal macrophages or wear particles, and no signs of metal sensitivity. [5]

In summary the information from the mid-term clinical retrievals of contemporary metal-on-metal prostheses demonstrates that the small amount of debris generated from well-functioning implants is well tolerated. Histological features consistent with a metal sensitivity response occur in a very small number of patients, but, since it can lead to osteolysis and/or revision, this is a serious, though rare complication. It is not clear if similar reactions occur in patients with other types of cobalt chromium alloy implants such as total knees.

In vitro Biocompatibility Testing With Cobalt Chromium Alloy Particles

Wear particles from metal-on-metal bearings are known to be smaller than can be resolved at the light microscope level, that is, most are less than 100 nanometers in length. [13,18,19] Presumably the particles seen by light microscopic analysis of periprosthetic tissue

from around metal-on-metal joints are the result of wear processes from sources other than the bearing, or may be the result of agglomeration of smaller particles. The composition of the particles is variable and includes a predominance of chromium oxide particles from the reactive outermost layers in the bearing surfaces, [4,11] and cobalt chromium alloy particles, most likely from the wear of the carbides on the bearing surfaces or from non-bearing surfaces. This highlights the need for excellent manufacturing and surgical implantation so that excessive wear-in, or unintended wear at impinging surfaces are minimized.

The nanometer-sized particles provide a huge surface area for in vivo corrosion. Since this is likely to have a significant impact on cellular interactions with the particle, it would be preferable to use nanometer–sized particles for biocompatibility studies. Unfortunately, these are not readily available to researchers and their extraction from periprosthetic tissues or hip simulator serum lubricants is technically difficult, time consuming, costly and is likely to yield insufficient amounts for controlled studies. For these reasons, researchers have been forced to use submicron to micron-sized particles of cobalt chromium alloy or cobalt and chromium salts that will break down in solution to create metallo-organic compounds. One group has solved this problem by generating large amounts of nanometer-sized cobalt chromium alloy particles for their own experiments using a pin-on-flat tribometer with water lubrication and filtering techniques. [20] These nanometer-sized cobalt chromium alloy particles were found to be cytotoxic to macrophage and fibroblast cell lines whereas particles approximately 5 to 10 microns in diameter had no such effect, supporting the notion that the surface area of the particle is critical to the biological effects intracellularly.

This highlights the findings from a number of in vitro particle/cell studies that the particle size, concentration, surface chemistry and shape may all be important to the cell

response. [7] Low to moderate concentrations of cobalt chromium alloy metal particles stimulate the release of cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α, and prostaglandin E, that can lead to periprosthetic osteolysis and aseptic loosening. [25] At higher concentrations, however, cobalt chromium alloy particles have been found to be cytotoxic. Haynes et al [25] compared the in vitro response of human monocytes to similar concentrations of 1 micron-sized particles of cast and forged cobalt chromium alloy, stainless steel, and titanium alloy. There was no difference in biological effects of the 2 cobalt chromium alloy materials and stainless steel as all were toxic to cells, while titanium alloy was not.

One confounding variable that makes it difficult to simulate the effects of clinically produced particles in an in vitro model is the fact that particles produced in vivo corrode and create a variety of organo-metallic wear species. [24] Haynes et al [26] attempted to study this phenomenon by comparing the response to fresh and aged (corroded) cobalt chromium alloy and stainless steel particles. Particles from 0.2 to 3 microns in diameter were exposed to cell culture media at physiological pH (7.2) or acidified after the addition of 1 M hydrochloric acid (to pH 4.5) for various times. The resulting corrosion was monitored by examining the supernatant using atomic absorption spectroscopy. They demonstrated that the release of soluble cobalt and chromium was greatest in the first hour, then markedly reduced but continued with time under physiological pH conditions (pH 7.2), while at pH 4.5 very little corrosion occurred after 24 hours. The pre-corroded (aged) particles of both metals were markedly less toxic to monocytes than freshly produced particles and appeared to stimulate the release of more IL-6 probably because the cells were less affected by the toxicity of the aged particles. This may explain why the tissue response in long-term retrievals appears to be relatively benign, while tissue necrosis

has been reported in short-term retrievals, even though the amounts of metal wear was low in both cases. [15, 17]

Catelas et al [14] used soluble metal salts to assess whether the toxicity response to cobalt chromium particles produced a necrotic or apoptotic mode of cell death. They incubated monocytes in growth medium containing 0–10 ppm Co^{2+} and 0–500 ppm Cr^{3+} for 24 and 48 hours then tested them for necrosis or apoptosis. At low concentrations of Co ions, cell viability remained high but at higher concentrations, apoptosis occurred within 24 hours. After 48 hours of exposure to cobalt ions, the rate of necrosis increased. Macrophages exposed to low concentrations of Cr ions died apoptotically while at higher concentrations, more necrosis occurred. This study might explain the appearance of relatively benign inflammatory responses around metal-on-metal hips, even when necrosis is present, because apoptosis is a "clean" form of cell death, whereas necrosis tends to induce an ongoing inflammatory response.

Different cellular responses to metal particles have been demonstrated in cells other than macrophages. Confluent primary human osteoblasts and MG63 osteoblast-like cells were incubated with particles of commercially pure titanium (CPTi), Ti-6Al-4V alloy, and cobalt chromium alloy of approximately one micron diameter.[32] All three types of particles were phagocytosed and both Ti alloy and cobalt chromium alloy caused a dose-dependent increase in cell number, while CPTi particles at the 1:10 dilution caused a maximal increase in cell number. Inflammatory mediator release was increased by all particles, but the magnitude of the effect was particle-dependent with cobalt chromium alloy having the most pronounced effect. Human bone derived cells were incubated with equivalent concentrations of these same types of particles in phagocytosable sizes 0.5-3.0 μm.[27] Although the levels of osteoclastogenic mediators was

higher in cells cultured with titanium alloy particles, cobalt chromium alloy particles were also shown to produce these mediators.

Cobalt and chromium particles from 2 to 15 microns in diameter were well tolerated by osteoblastic cell lines, but at high concentration, the growth and metabolism of the cells was affected. [1] Suppression of collagen synthesis following phagocytosis by osteoblasts of chromium orthophosphate (a corrosion product from cobalt-chromium alloy implants) was also shown by Vermes et al. [42] The cells released interleukin-6 which is a known osteoclast promoter. The authors suggest that the combined effect of the depletion of osteoblast activity and the activation and differentiation of osteoclasts would be decreased bone formation with possible implant loosening. These studies lend further support to observations of a complex interplay between bone forming and resorbing cells in the presence of particulate debris in periprosthetic tissues.

It is important to study the effects of particles on human cells and, where possible, to use cells from patients with implants. Lee et al [31] studied the responses to particles of commercially pure titanium and chromium orthophosphate by human peripheral blood monocytes from 10 normal volunteers and 15 patients with total hip replacements. Eight of these were well functioning at average 88 months post-operatively, but 5, with a variety of cemented and cementless implants, had failed with loosening and/or osteolysis at average 105 months post-operatively. The mononuclear cells from patients with total hip replacements appeared to be sensitized to metal particles in comparison with control subjects without an implant. The chromium orthophosphate corrosion product was found to be a potent macrophage/ monocyte activator and there were no significant differences in the responses of cells from patients with and without osteolysis. This study highlights the need to reduce metal wear products from all sources, including corrosion at the ball/stem taper.

Metal Sensitivity

As mentioned previously, metal sensitivity is a long-standing concern with metal-on-metal implants that remains a relevant issue in contemporary metal-on-metal total joints. Although this issue has been addressed sporadically since the introduction of cobalt based alloys in medicine, in vitro models of metal sensitivity have not been developed, although studies of the responses of isolated cells give useful information that may help predict in vivo reactions. [23,34] Hallab et al [22] have shown that lymphocytes from patients with well-functioning metal-on-metal implants responded to a higher degree to soluble metal (nickel, cobalt, chromium, titanium, aluminum, vanadium) challenge compared with cells from patients with metal-on-polyethylene bearings or control patients with osteoarthritis, although all groups showed some degree of metal reactivity. There was also a strong relationship between the serum cobalt ion levels and lymphocyte reactivity to the metal, supporting the authors' hypothesis that metal reactivity increases with increased metal exposure, although they caution that there is no clear association between these results and clinical outcome.

This last point is perhaps a timely reminder that caution must be applied to the over-interpretation of the results of in vitro studies to predict clinical results, particularly when differences in cell types, particle size and shape, incubation conditions and test methods can vary markedly between research groups. Clearly the interactions between metal wear products and the variety of cells in the local and distant tissues are complex and likely to be affected by multiple factors, only a few of which can be even partially examined by in vitro testing.

Conclusions

- Implant retrieval studies of long-term metal-on-metal implants show that cobalt chromium alloy particulate is generally well tolerated by the body within specific limits
- Cobalt chromium alloy particulates appear to elicit a lower tissue histiocyte response than do polyethylene and cement particles, consistent with the lower incidence of periprosthetic osteolysis around metal-on-metal implants
- Autopsy retrieval studies show that patients with well-functioning metal-on-metal implants show little evidence of local or systemic adverse effects, even after several decades of implantation
- Hip replacement patients' circulating lymphocytes may be sensitized by the presence of metal implants compared with lymphocytes in patients without implants, but the effect on clinical outcome is unclear
- Sensitivity to metals used in total hip replacements is a rare cause of failure
- Correlation of the in vitro and in vivo response to metal wear debris is limited due to the difficulty of extraction and collection of sufficient quantities of small (nanometer) particles required for these studies
- The amount of wear products from total hip replacements needs to be held to a minimum, regardless of their source, e.g., particulate wear debris, corrosion, fretting, etc. because in vitro studies show that large amounts of cobalt chromium alloy particulates and related dissolution products can be cytotoxic
- Minimizing debris generated from articulating and non-articulating (impingement) surfaces is one method to reduce local and systemic debris effects

Bibliography

1. Allen MJ, Myer BJ, Millett PJ, Rushton N: The effects of particulate cobalt, chromium and cobalt-chromium alloy on human osteoblast-like cells in vitro. J Bone Joint Surg 79B:475-482, 1997.

2. Al-Saffar N: Early clinical failure of total joint replacement in association with follicular proliferation of B-lymphocytes: a report of two cases. J Bone Joint Surg 84-A:2270-2273., 2002.

3. Beaule PE, Campbell P, Mirra J, et al: Osteolysis in a cementless, second generation metal-on-metal hip replacement. Clin Orthop 386:159-165., 2001.

4. Buscher R, Tager G, Dudzinski W, et al: Subsurface microstructure of metal-on-metal hip joints and its relationship to wear particle generation. J Biomed Mater Res B Appl Biomater 72:206-214., 2005.

5. Campbell P, McKellop H, Alim R, et al: Metal-On-Metal Hip Replacements: Wear Performance and Cellular Response To Wear Particles. In Disegi JA, Kennedy RL, Pilliar R (eds). *Cobalt-Base Alloys for Biomedical Applications, ASTM STP 1365.* West Conshohocken, PA,, American Society for Testing and Materials p193-209, 1999.

6. Campbell P, Mirra J, "Lymphocytic Vasculitis Associated Lesions Around Metal-Metal Total Hips," *Society for Biomaterials 28th Annual Meeting*, 2002

7. Campbell P, Shen FW, McKellop H: Biologic and tribologic considerations of alternative bearing surfaces. Clin Orthop 418:98-111., 2004.

8. Campbell P, Urban RM, Catelas I, et al: Autopsy analysis thirty years after metal-on-metal total hip replacement. A case report. J Bone Joint Surg 85-A:2218-2222., 2003.

9. Campbell PA, Wang M, Amstutz HC, Goodman SB: Positive cytokine production in failed metal-on-metal total hip replacements. Acta Orthop Scand 73:506-512., 2002.

10. Case CP, Langkamer VG, James C, et al: Widespread dissemination of metal debris from implants. J Bone Joint Surg 76:701-712, 1994.

11. Catelas I, Campbell P, Bobyn D, et al, "Does a Hip Simulator Generate Metal-Metal Wear Particles the Same as in Vivo?," *48th Annual Meeting of the Orthopaedic Research Society*, 2002

12. Catelas I, Campbell PA, Dorey F, et al: Semi-quantitative analysis of cytokines in MM THR tissues and their relationship to metal particles. Biomaterials 24:4785-4797, 2003.

13. Catelas I, Medley JB, Campbell PA, et al: Comparison of in vitro with in vivo characteristics of wear particles from metal-metal hip implants. J Biomed Mater Res 70B:167-178., 2004.

14. Catelas I, Petit A, Vali H, et al: Quantitative analysis of macrophage apoptosis vs. necrosis induced by cobalt and chromium ions in vitro. Biomaterials 26:2441-2453., 2005.

15. Davies AP, Willert HG, Campbell PA, et al: An unusual lymphocytic perivascular infiltration in tissues around contemporary metal-on-metal joint replacements. J Bone Joint Surg 87:18-27, 2005.

16. Delaunay CP: Metal-on-metal bearings in cementless primary total hip arthroplasty. J Arthroplasty 19:35-40., 2004.

17. Doorn PF, Campbell PA, Amstutz HC: Metal versus polyethylene wear particles in total hip replacements. A review. Clin Orthop 329 Suppl:S206-216, 1996.

18. Doorn PF, Campbell PA, Worrall J, et al: Metal wear particle characterization from metal on metal total hip replacements: Transmission electron microscopy study of periprosthetic tissues and isolated particles. J Biomed Mater Res 42:103-111, 1998.

19. Firkins PJ, Tipper JL, Saadatzadeh MR, et al: Quantitative analysis of wear and wear debris from metal-on-metal hip prostheses tested in a physiological hip joint simulator. Biomed Mater Eng 11:143-157., 2001.

20. Germain M, Hatton A, Williams S, et al: Comparison of the cytotoxicity of clinically relevant cobalt-chromium and alumina ceramic wear particles in vitro. Biomaterials 24:469-479, 2003.

21. Granchi D, Ciapetti G, Stea S, et al: Cytokine release in mononuclear cells of patients with Co-Cr hip prosthesis. Biomaterials 20:1079-1086, 1999.

22. Hallab N, Anderson S, Caicedo M, et al: Immune responses correlate with serum-metal in metal-on-metal hip arthroplasty. J Arthroplasty 19:88-94, 2004.

23. Hallab N, Merritt K, Jacobs JJ: Metal sensitivity in patients with orthopaedic implants. J Bone Joint Surg 83A:428-436., 2001.

24. Hallab NJ, Jacobs JJ, Skipor A, et al: Systemic metal-protein binding associated with total joint replacement arthroplasty. J Biomed Mater Res 49:353-361, 2000.

25. Haynes DR, Boyle SJ, Rogers SD, et al: Variation in cytokines induced by particles from different prosthetic materials. Clin Orthop 362;223-230, 1998.

26. Haynes DR, Crotti TN, Haywood MR: Corrosion of and changes in biological effects of cobalt chrome alloy and 316L stainless steel prosthetic particles with age. J Biomed Mater Res 49:167-175, 2000.

27. Haynes DR, Crotti TN, Potter AE, et al: The osteoclastogenic molecules RANKL and RANK are associated with periprosthetic osteolysis. J Bone Joint Surg 83B:902-911., 2001.

28. Huk OL, Catelas I, Mwale F, et al: Induction of apoptosis and necrosis by metal ions in vitro. J Arthroplasty 19:84-87., 2004.

29. Jantsch S, Schwägerl W, Zenz P, et al: Long-term results after implantation of the McKee-Farrar total hip prostheses. Arch Orthop Trauma Surg 110:230-237, 1991.

30. La Budde JK, Orosz JF, Bonfiglio TA, Pellegrini VD, Jr.: Particulate titanium and cobalt-chrome metallic debris in failed total knee arthroplasty. A quantitative histologic analysis. J Arthroplasty 9:291-304, 1994.

31. Lee S-H, Brennan FR, Jacobs JJ, et al: Human monocyte/macrophage response to cobalt-chromium corrosion products and titanium particles in patients with total joint replacements. J Orthop Res 15:40-49, 1997.

32. Lohmann CH, Schwartz Z, Koster G, et al: Phagocytosis of wear debris by osteoblasts affects differentiation and local factor production in a manner dependent on particle composition. Biomaterials 21:551-561, 2000.

33. Long WT, Dorr LD, Gendelman V: An American experience with metal-on-metal total hip arthroplasties: a 7-year follow-up study. J Arthroplasty 19:29-34., 2004.

34. Merritt K, Brown SA: Distribution of cobalt chromium wear and corrosion products and biologic reactions. Clin Orthop 329 Suppl:S233-243, 1996.

35. Migaud H, Jobin A, Chantelot C, et al: Cementless metal-on-metal hip arthroplasty in patients less than 50 years of age: comparison with a matched control group using ceramic-on-polyethylene after a minimum 5-year follow-up. J Arthroplasty 19:23-28., 2004.

36. Niki Y, Matsumoto H, Otani T, et al: Screening for symptomatic metal sensitivity: a prospective study of 92 patients undergoing total knee arthroplasty. Biomaterials 26:1019-1026., 2005.

37. Schmalzried TP, Peters PC, Maurer BT, et al: Long-duration metal-on-metal total hip arthroplasties with low wear of the articulating surfaces. J Arthroplasty 11:322-331, 1996.

38. Shimmin AJ, Back D: Femoral neck fractures following Birmingham hip resurfacing: A NATIONAL REVIEW OF 50 CASES. J Bone Joint Surg 87:463-464., 2005.

39. Szuszczewicz ES, Schmalzried TP, Petersen TD: Progressive bilateral pelvic osteolysis in a patient with McKee-Farrar metal-metal total hip prostheses. J Arthroplasty 12:819-824, 1997.

40. Urban R, Jacobs J, Tomlinson M, Galante J, "Renal tubular chromium deposition in patients with failed or long term joint replacement," *Trans 47th Annual Meeting, Orthopaedic Research Society*, 165 (2001.)

41. Urban RM, Tomlinson MJ, Hall DJ, Jacobs JJ: Accumulation in liver and spleen of metal particles generated at nonbearing surfaces in hip arthroplasy. J Arthroplasty 19:94-101, 2004.

42. Vermes C, Glant TT, Hallab NJ, et al: The potential role of the osteoblast in the development of periprosthetic osteolysis: review of in vitro osteoblast responses to wear debris, corrosion products, and cytokines and growth factors. J Arthroplasty 16:95-100., 2001.

43. Willert H, Buchorn G, Fayaayazi A, Lohmann C: Histopathological changes around metal/metal joints indicate delayed type hypersensitivity. Preliminary results of 14 cases. Osteologie 9:2-16, 2000.

44. Willert HG: Tissue reactions around joint implants and bone cement. In Chapchal G (ed). Arthroplasty of the Hip. Stuttgart, Georg Thieme 11-21, 1973.

45. Willert H-G, Buchhorn GH, Dipl-Ing, et al: Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. a clinical and histomorphological study. J Bone Joint Surg 87:28-36, 2005.

46. Willert H-G, Buchhorn GH, Semlitsch M: Particle disease due to wear of metal alloys. Findings from retrieval studies. In Morrey BF (ed). Biological, Material, and Mechanical Considerations of Joint Replacement, Bristol-Myers Squibb/Zimmer Orthopaedic Symposium Series,. New York, Raven Press, Ltd. 129-146, 1993.

47. Zahiri CA, Schmalzried TP, Ebramzadeh E, et al: Lessons learned from loosening of the McKee-Farrar metal-on-metal total hip replacement. J Arthroplasty 14:326-332, 1999.

48. Zaoussis AL, Patikas AF: Experience with total hip arthroplasty in Greece, the first 20 years. A particular reference to long-term results with the McKee-Farrar technique. Clin Orthop 246:39-47, 1989.