Appendix 2
Unpublished Reports

APPENDIX 2

UNPUBLISHED REPORTS

Metal Ion Release from Metal on Metal Hip Replacement Implants
Information in Support of Downclassification

Dr Jim Nevelős. December 2004

Introduction

Potential theoretical concerns remain about the long term effects of metal ions released from metal implants into the body. In particular, metal on metal bearings for hip replacement have been under scrutiny since their inception in the 1930s. This relates to hypersensitivity, carcinogenesis and, more recently, possible genetic mutations and effects on reproduction. Metal on metal hip bearings are manufactured from Cobalt Chrome alloys exclusively, the composition of which is governed by both ASTM and ISO standards. There are essentially two sets of standards, one for cast alloys and one for forged alloys the details of which are shown in Figure 1.

Table 1 Chemical Composition (% m/m) of Alloys used for Metal – Metal Hip Bearings.

	ASTM F75 Casting Alloy	BS/ISO 7252-4 Casting Alloy	ASTM F1537 Alloy 1 (Low Carbon) Forged	ASTM F1537 Alloy 2 (High Carbon) Forged	ASTM F1537 Alloy 3 (Dispersion Strengthened) Forged
Chromium	27 - 30	26.5 – 30	26 - 30	26 - 30	26 - 30
Molybdenum	5 - 7	4.5 – 7	5 - 7	5 - 7	5 - 7
Carbon	0.35 max	0.2 – 0.35	0.14 max	0 15 - 0 35	0.14 max
Nickel	0.5 max	1 max	1 max	1 max	1 max
Iron	0.75 max	1 max	0.75 max	0.75 max	0.75 max
Manganese	1 max	1 max	1 max	1 max	1 max
Silicon	1 max	1 max	1 max	1 max	1 max
Tungsten	0.2 max	n/s	n/s	n/s	n/s
Phosphorus	0 02 max	n/s	n/s	n/s	n/s
Sulphur	0.01 max	n/s	n/s	n/s	n/s
Nitrogen	0.25 max	n/s	0 25 max	0.25 max	0.25 max
Aluminium	0.1 max	n/s	n/s	n/s	0.3-1
Titanium	0.1 max	n/s	n/s	n/s	n/s
Boron	0.01 max	n/s	n/s	n/s	n/s
Lanthanum	n/s	n/s	n/s	n/s	0.03-0.2
Cobalt	Balance	Balance	Balance	Balance	Balance

The major constituents are, of course, cobalt (~60%) and chromium (~30%) and therefore the primary ions released into the body from these devices are cobalt and chromium. There are subtle differences between the various alloys which relate to their processing methods. Cast alloys are typically (but not exclusively) used for hip resurfacing prostheses (and therefore the associated large diameter total hip replacements which use the same monobloc acetabular components) whilst forged alloys are typically (but not exclusively) used for conventional 28 and 32mm total hip replacement. Of the minor alloying elements, the most significant is carbon. High carbon contents (0.15-0.35%) lead to the precipitation of carbide phases in the material. These carbides are associated with increased wear resistance although the precise volume fraction and morphology are influenced by processing methods. An analysis of the effect of carbon content and carbide morphology on wear was recently published by Nevelos *et al*[1]. The majority of metal on metal total hips are, however manufactured from a high carbon forged cobalt chrome pair or a mix with one low carbon and one high carbon component.

Background Information: Cobalt and Chromium

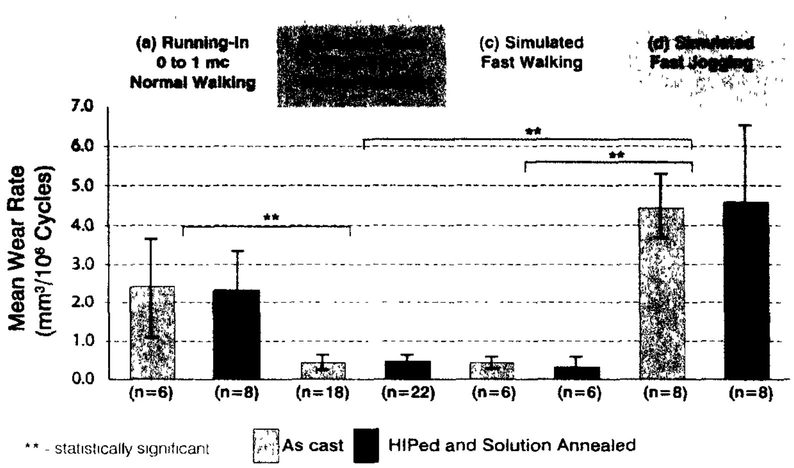
"**Cobalt** is a relatively rare magnetic element with properties similar to iron and nickel. The two valance states are cobaltous (II) and cobaltic (III) and the former is the most common valance used in the chemical industry. Cobalt occurs in nature primarily as arsenides, oxides, and sulfides. Most of the production of cobalt involves the metallic form used in the formation of cobalt superalloys. The term "hard metal" refers to compounds containing tungsten carbide (80-95%) combined with matrices formed from cobalt (5-20%) and nickel (0-5%). For the general population, the diet is the main source of exposure to cobalt. In the occupational setting, exposure to cobalt alone occurs primarily during the production of cobalt powders. In other industrial exposures (e.g., hard metal, diamond polishing), additional agents (tungsten) modulate the toxicity of cobalt. Cobalt is an essential element necessary for the formation of vitamin B12 (hydroxocobalamin); however, excessive administration of this trace element produces goiter and reduced thyroid activity. In 1966, the syndrome "beer drinker's cardiomyopathy" appeared in Quebec City, Canada, and was characterized by pericardial effusion, elevated hemoglobin concentrations, and congestive heart failure. An interstitial pulmonary fibrosis has been associated with industrial exposure to hard metal dust (tungsten and cobalt), but not to cobalt alone. Exposure to cobalt alone produces an allergic contact dermatitis and occupational asthma. Treatment of cobalt toxicity is primarily supportive." Reproduced abstract from: Barceloux DG. 'Cobalt' J Toxicol Clin Toxicol. 1999;37(2):201-6. (Copyright permission not sought).

"**Chromium** occurs primarily in the trivalent state (III), which is the most stable form, or in the hexavalent state (VI), which is a strong oxidizing agent. Elemental chromium (0) does not occur naturally on earth. Trivalent chromium (III) is an essential trace metal necessary for the formation of glucose tolerance factor and for the metabolism of insulin. Commercial applications of chromium compounds include tanning (III), corrosion inhibition, plating, glassware-cleaning solutions, wood preservatives (VI), manufacture of safety matches, metal finishing (VI), and the production of pigments (III, VI). Hexavalent chromium (VI) contaminated local soil when chromium waste slag was part of the fill material present in residential, public, and industrial areas. In some urban areas, about two-thirds of the chromium in air results from the emission of hexavalent chromium from fossil fuel combustion and steel production. The remaining chromium in air is the trivalent form. The residence time of chromium in air is < 10 days, depending on the particle size. Trivalent compounds generally have low toxicity and the gastrointestinal tract poorly absorbs these compounds. Hexavalent chromium is a skin and mucous membrane irritant and some of these hexavalent compounds are strong corrosive agents. Hexavalent chromium compounds also produce an allergic contact dermatitis characterized by eczema. Sensitivity to trivalent compounds is much less frequent, but some workers may react to high concentrations of these compounds. Hexavalent chromium is recognized by the International Agency for Research on Cancer and by the US Toxicology Program as a pulmonary carcinogen. The increased risk of lung cancer occurs primarily in workers exposed to hexavalent chromium dust during the refining of chromite ore and the production of chromate pigments. Although individual studies suggest the possibility of an excess incidence of cancer at sites outside the lung, the results from these studies are inconsistent." Reproduced abstract from: Barceloux DG. 'Chromium' J Toxicol Clin Toxicol. 1999;37(2):173-94. (Copyright permission not sought).

Wear Data

Metal ions are released into the body via a corrosion process. There may be some corrosion of the bulk components but the largest surface area for corrosion may come from the wear debris produced during normal activities. Therefore an understanding of the wear rates, process and debris produced is useful. Hip simulator studies have shown that metal on metal bearings routinely have a 'running-in' period in the first 0.5 – 1 million cycles, commonly approximated to be the first year of clinical usage. For example, this was demonstrated in the recent study on 40mm resurfacing bearings published by Bowsher *et al*[2]. This study showed higher 'running in' wear for both as cast and HIPed and solution annealed high carbon cobalt chrome bearings. This could lead to elevated ion release in the first year or so post-operatively. One could then reasonably expect a decrease in ion levels after this period as the wear rates decreased.

Figure 2. Wear Results from Bowsher *et al*[2] 2002.



This type of bi-phasic wear pattern has been reproduced in many other simulator studies such as those by Goldsmith *et al*[3], Scholes *et al*[4] and Chan *et al*[5]. The *in vitro* and *in vivo* wear properties of metal on metal bearings are discussed in detail in a separate document, 'Wear of Metal on Metal Hip Replacement Implants,' which is also part of this downclassification submission.

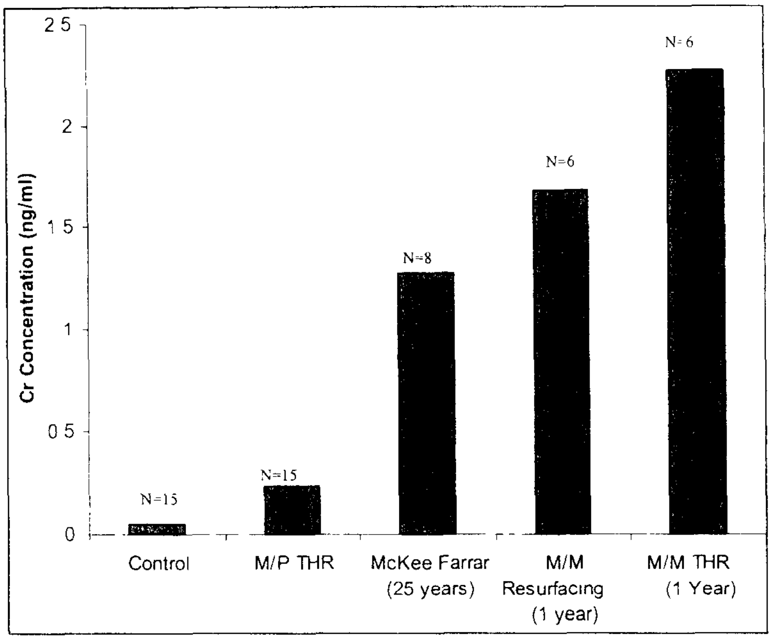
Published Data on Metal Ion Release

Metal ion release into the body is an inevitable consequence of implanting any metal device into the body. Case *et al*[6] reported, in a post mortem study, widespread dissemination of metal wear debris and elevated metal levels from conventional replacement joints (with metal on polyethylene articulations) and to a lesser extent also from dynamic hip screws. Metal on metal bearings for hip joint replacement, despite their low wear rate, have the potential for increased levels of ion release into the body as a result of the wear debris formed from the articulation. The clinical effects of this ion release are the subject of current debate. An excellent recent paper from MacDonald *et al*[7] has reviewed the methods of collection and analysis of metal ion levels. Published studies have used whole blood, serum, urine, synovial fluid, erythrocytes, local and distant tissues for measuring ion levels. There are also errors inherent in the methodologies with some techniques proving more accurate than others (inductively coupled plasma mass spectrometry (ICP-MS) as compared to graphite furnace atomic absorption spectrophotometry (GFAAS))[8]. It has been estimated that 250,000 metal on metal total hip replacements have been implanted worldwide, only a small fraction of which have been studied for ion release. Therefore, while it is difficult to draw absolute conclusions, these studies are still useful in estimating the realistic amount of ion release into the body.

There have been many studies about the ion release from all types of metal implants. For example, Jacobs *et al*[9] reported substantially elevated serum chromium levels with both non-modular and modular femoral nails as compared to a control group. The modular nails had markedly higher levels than the non-modular group probably due to increased fretting corrosion at the modular junctions. In another study, Harding *et al*[10] found no difference in ion release with a standard (cobalt chrome) hip stem (Oxford Universal Hip, Corin); a modular hip stem system in which the stem was allowed to slide in the proximal section; and a standard (cobalt chrome) cemented hip (Cenator, Corin).

Hip prostheses with metal on metal bearings, however, do release more metal ions into the body than hip prostheses with metal on UHMWPE bearings. There have been some studies in this area. For example Savarino *et al*[11] followed three groups of patients (metal on metal; metal on UHMWPE and a control group) and found significantly higher serum cobalt and chromium levels in the metal on metal group compared to the metal on UHMWPE and control groups. Jacobs *et al* and others[12, 13, 14, 15] also published data on the relative serum chromium concentrations of various hip articulations with controls vs. metal on UHMWPE, metal on metal at 25 years (McKee Farrar), metal on metal resurfacing hip replacement at 1 years and metal on metal total hip replacement at 1 year. The approximate relative ion levels are shown in Figure 1.

Figure 1. Published Ion Concentrations[12-15].

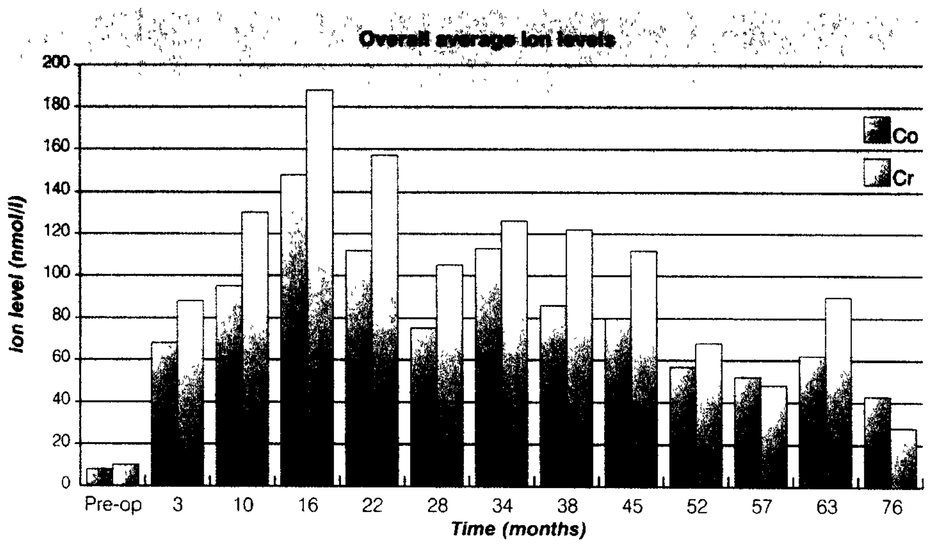


These results have been mirrored in other studies in that the short-term ion levels tend to be relatively high while the longer-term levels tend to be lower. It is interesting that the resurfacing hip replacement levels are slightly lower than the total hip levels at 1 year. However it should be noted that there were relatively few data points for these levels and therefore no statistical analysis was performed.

Brodner *et al*[16] published a study looking at serum cobalt levels up to 5 years following 28mm Metasul® total hip replacement. The stems and sockets were titanium alloy and pure titanium respectively and the bearings were randomised to be either the Metasul® metal on metal or a conventional ceramic on polyethylene. The median serum cobalt concentration was 1µg/l at one year after surgery in the Metasul group and 0.7µg/l at 5 years after surgery. The control ceramic on polyethylene group cobalt levels remained below the detection limit throughout the study. There did not appear to be an effect of the 'running in' wear commonly seen in hip simulator studies.

Reddy *et al*[17] published serum cobalt and chromium levels from a cohort of 39 patients with modern metal on metal resurfacing devices (with an identical bearing to a large diameter metal on metal total hip replacement currently being marketed in Europe) who had been followed for up to 7 years. The results showed, for the vast majority of patients, an initial rise in ion levels followed by a slow decrease over time. The results of the general population are shown in Figure 3.

Figure 3. Metal Ion Release from Resurfacing Implants (Reddy *et al*[17])



Also of interest is that there is a wide scatter of ion levels across the patient groups, again possibly indicating the uncertainties in measuring these tiny amounts of trace ions. For comparison if we average the levels shown in Figure 3 to an arbitrary 100nmol/l, then this equates to concentrations of 5.9μg/l for Cobalt and 5.2μg/l for chromium which is slightly higher than the levels shown by Brodner *et al*[16].

Factors such as implant position, activity levels, lifestyle and even geographical area (content of the water supply etc.) can have an effect on the ion levels recorded in patients.

Figure 4 shows the raw data for the above ion level study highlighting this level of scatter, the lines are polynomial best fit lines showing the overall trend.

Figure 4. Scatter graph of Raw Data from Reddy *et al*[17], AAOS, 2003.

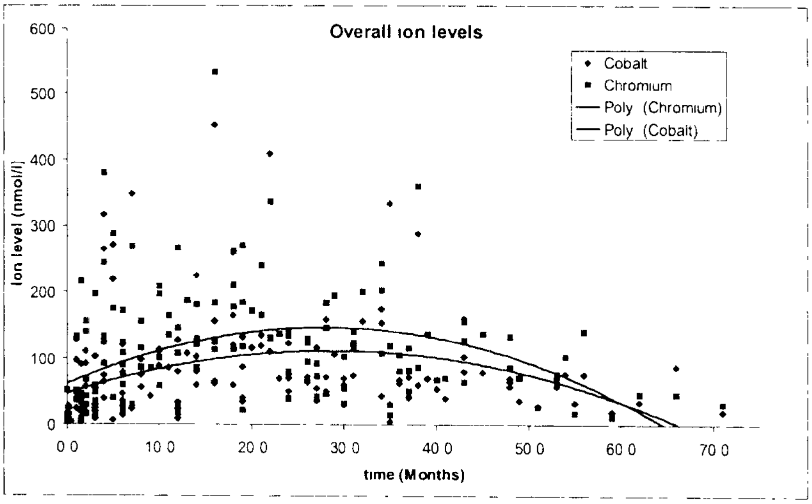


Figure 4 highlights the fact that there is an inherently high level of scatter in these types of studies as the levels of cobalt and chromium could be affected by many factors such as activity levels, bearing diameter and patient health and diet. It has been proposed that running-in wear may be higher for large diameter metal-metal bearings due to the larger contact areas involved and the generally higher radial clearances, however the much lower steady state wear rates may lead to a lower overall wear volume after about 5 million cycles (1-2 years in an active patient).

Clarke *et al*[18] published a study which directly compared the serum levels of cobalt and chromium for both hip resurfacing and total hip replacement with 28mm metal on metal bearings. There were 22 patients in each group which were matched for date after surgery within 6 months; activity levels and body mass to within 10Kg. The results showed higher serum levels of both cobalt and chromium for the resurfacing group at a median of 16 months after surgery. The levels for the resurfacing patients were lower than those in the study by Reddy *et al*[17] at approximately the same time point post-operatively.

MacDonald[7] collated the majority of published studies in a table which is reproduced here as Table 2 (please note this is a direct reproduction from the paper by MacDonald[7], copyright permission has not been sought).

Table 2 Published Blood Cobalt Levels of Metal-on-Metal Implants

Author	Implant	Analytic Technique	Blood Sample	No. of Implants	Time in vivo (yrs)	Median Cobalt Level (μg/L)
Coleman et al [19]	C cast alloy	Neutron Activation Analysis	Whole Blood	9	1	6.5**
Jacobs et al [15]	McKee-Farrar	AAS	Serum	8	25	0.9**
Brodner et al [20]	Metasul*	AAS	Serum	27	1	1.1
Schaffer et al [21]	Sikomet-SM21†	AAS	Whole Blood	76	1–3	1.5
Skipor et al [22]	Conserve Plus‡	AAS	Serum	21	1	1.1
MacDonald et al [23]	M²a§	ICP-MS	Erythrocytes	22	3.2	1.1
Clarke et al [18]	Ultima‖	ICP-MS	Serum	22	1.3	1.3
	Birmingham Resurfacing¶	ICP-MS	Serum	16	1.3	2.1
	Cormet 2000 Resurfacing#	ICP-MS	Serum	6	1.3	3 0
Brodner et al [16]	Metasul*	AAS	Serum	36	5	0.7
Savarino et al [24]	Metasul*	AAS	Serum	15	2	0.88
				15	4 3	0.81

Abbreviations: AAS, atomic absorption spectrophotometry; ICP-MS, inductively coupled plasma mass spectrometry.

*Zimmer GmbH, Winterthur, Switzerland.
†Sikov Medizintechnik, Vienna, Austria.
‡Wright Medical Technology, Arlington, TN, USA.
§Biomet, Warsaw, IN, USA.
‖Johnson & Johnson, Leeds, UK.
¶Midland Medical Technologies, Birmingham, UK.
#Corin Surgical, Cirencester, UK.
**Mean Co levels reported

The results of these studies are not conclusive. There appears to be a trend for resurfacing patients having higher ion levels in the short term than the THR patients which may be related to a higher running in wear for these bearings. Typical ion levels in these patients is of the order of 50-150 nmol/l (~5μg/l)[17, 18] which is slightly higher than the approximate value of 1μg/l for the Metasul bearing from the studies shown in Table 2. The biological exposure index (BEI) for cobalt in blood for occupational exposure is 1μg/l as recommended by the American Conference of Governmental Industrial Hygienists[25]. However this value is set for workers exposed to cobalt via inhalation rather than direct internal exposure via an endoprosthesis. The beer drinkers incident referred to on page three involved a group of nutritionally deficient beer drinkers who consumed beer which had cobaltous chloride as a foam stabiliser at concentrations of around 1mg/l[26] leading to daily intakes of 5-10mg, an exposure many orders of magnitude larger than those seen in association with metal on metal hip implants. The ACGIH Threshold Limit Value / Time Weighted Average (TLV/TWA) for current occupational exposure is 20μg/m^3 which corresponds to a daily intake of 133mg/day assuming complete deposition and absorption, a 70Kg individual and a breathing rate of 20m^3 per day. This would equate to a wear volume of 14.9mm^3 being released from a metal on metal hip joint and completely absorbed <u>per day</u>. Average wear rates for metal on metal hips are less than 1mm^3 <u>per year</u>. These calculations would appear to indicate that the current guidelines on exposure by inhalation may not be applicable to exposure from implants. However, they illustrate the fact that the exposure to cobalt from metal on metal hip joints is highly unlikely to produce a toxic reaction, although there are other effects to be considered.

Published Data on Carcinogenesis

Metal wear debris has long been feared to be a potential of carcinogenesis. There have been several epidemiological studies that do not show any increase in cancers compared to control groups with no implants. For metal on metal hip joints Visuri *et al*[27] published a study that looked specifically at the incidence of cancers in patients with metal on metal total hip replacements (698 McKee-Farrar devices) and 1585 conventional metal on UHMWPE devices in Finland as compared to a matched general population. The net outcome was no statistically significant increase in cancers with either type of prostheses over a 15.7 and 12.5 mean follow-up period respectively. Tharani *et al*[28] conducted a meta-analysis of studies which evaluated the incidence of cancers in patients with and without joint replacements of various types. The conclusion of this study was there was no causal link between joint replacement and cancer.

Published Data on Genetic Damage

It would therefore seem unlikely therefore that there is a danger of toxicity or cancer associated with metal on metal hip replacements. The possibility of genetic damage has been raised relatively recently. This is perhaps the last remaining concern with metal on metal hip replacements, given that they are now being implanted in patients of child bearing age. (Although there is some evidence that these ions do not cross the placental barrier[29]). Pilger *et al*[30] published a study using markers of oxidative DNA damage and the frequency of sister chromatid exchanges in lymphocytes to test a possible relationship between the concentrations of chromium or cobalt and the induction of cytogenetic modifications in 46 patients with total hip replacements. A broad range of individual levels of metals was observed in the patients: chromium in blood, 1.59-14.11 microg/L; chromium in urine, 0.79-93.80 microg/24 h; cobalt in blood, 0.77-37.80 microg/L; cobalt in urine, 2.59-166.94 microg/24 h. By linear regression analysis, no significant correlation between oxidative DNA markers or sister chromatid exchange (SCE) and the concentrations of metals was found. However, cobalt in blood as well as 8-OHdG in urine were higher in patients with implants 3-4 yrs old as compared to patients with implants 1-2 yr old. Smoking significantly increased the frequency of SCE. The data did not indicate a dependence of oxidative DNA markers in urine or SCE on the levels of chromium or cobalt in patients with total hip replacements.

The conclusion of this study would appear to be that there is not necessarily a genotoxic effect of metal ion release from metal on metal hip prostheses.

In contrast to these findings, Professor Case has published several studies[31, 32, 33] investigating the incidence of aneuploidy and chromosome translocations as related to metal ion release from orthopaedic implants (N.B. Aneuploidy is the condition of having less than or more than the normal diploid number of chromosomes, and is the most frequently observed type of cytogenetic abnormality). Titanium implants were shown to produce a five fold increase in aneuploidy with no change in chromosome translocations, cobalt chrome implants have a lesser (two and a half fold) increase in aneuploidy but with a three and a half fold increase in chromosome translocations. The clinical effects of these abnormalities is yet to be established.

Hypersensitivity

There have been some recent reports of hypersensitivity around metal on metal hip implants[34]. The incidence was extremely low, however. The sensitivity reaction manifests itself with reoccurrence of pain often accompanied by limping, effusion from the joint, dislocation or subluxation. At revision there is commonly effusion and large fibrin masses sometimes in connection with bursa formation. When the bearing is exchanged for another combination the symptoms resolve quickly, if a second metal-metal articulation was implanted the symptoms persisted.

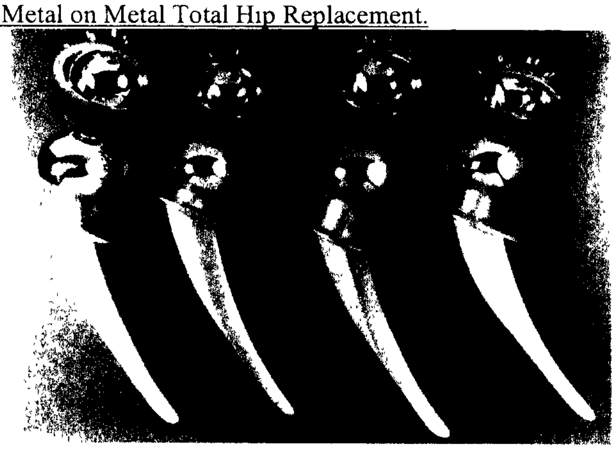
This type of reaction is very infrequent and is the subject of much research at present.

Published Clinical Data on Metal on Metal Articulations

1st Generation devices

The most commonly reported 1st generation metal on metal hips are of the McKee Farrar design shown in Figure 5. Both the femoral and acetabular components were cemented in place with the stem obviously being based on the existing Thompson hemi-arthroplasty.

Figure 5 McKee Farrar Metal on Metal Total Hip Replacement.



There are several studies which have reviewed the survivorship of these devices. This is not intended to be an exhaustive review as several other authors have produced more in depth analyses of the survival of 1st generation implants, however it is useful to briefly review the main messages from the literature. Table 3 contains some published survivorship rates of McKee Farrar prostheses.

Table 3. Survivorship of McKee Farrar Prostheses

Study	No. of Hips (no. of patients)	Average Age at Primary Op (range)	Survivorship	Hip Scores
Brown *et al* (2002)[35]	153 (129)	61 (28-85)	84% at 20 yrs 74% at 28 yrs	N/S
Jacobsson *et al* (1996)[36]	107 (N/S)	N/S	77% at 20yrs	82 at 12 yrs (Harris) 75 at 20 yrs (Harris
Visuri T (1987)[37]	511	N/S	82% at 10 years (aseptic loosening) 76% at 10 years (total)	N/S
August *et al* (1986)[38]	230 out of 808 reviewed	N/S	N/S	49% good or excellent at average 13.9 yrs 78% little or no pain
Dandy *et al* (1975)[39]	1042	N/S	93.4% at 2 yrs	N/S

N/S – not stated

The data in table 2 is consistent with most author's assertions that the pattern of failure with 1st generation metal on metal was a substantial number of early failures with fewer long term failures than with metal on polyethylene hip replacements. For example, the study by Jacobsson *et al*[36] is a comparative study with the Charnley prosthesis, with the McKee Farrar prosthesis demonstrating superior (if not statistically significantly so) survivorship of 77% compared to 73% at 20 years. With all of these studies however, there are questions over the total number of hips studied as compared to the numbers implanted. For example August *et al*[38] only reviewed 230 out of 808 prostheses which casts some doubts about the exact outcomes of these devices. One probable cause, of at least some, of the early failures was that the heads were slightly larger than the cups leading to equatorial contact and therefore increased friction which could have caused the prosthetic components to loosen. This was shown by Walker and Gold in 1971 (reprinted in CORR in 1996[40]) in a series of early McKee-Farrar retrievals.

In contrast, modern metal on metal hip replacements are followed up much more rigorously. Modern metal on metal total hip replacement was lead by the development of the Metasul® device by Sulzer Medica (now Zimmer) which was first used clinically in 1988 in Europe and was approved by the FDA for general sale in the USA in 1998. Recently Dorr *et al*[41] have published their experience with this device some of which was gained via the investigational device exemption (IDE) study for this device in the USA. 311 Metasul bearings were implanted in parallel with a group of conventional ceramic on polyethylene hips. The number (and modes) of failures in both groups was almost identical with an overall survivorship rates of 97.1% and 97.4% respectively (excluding infections) for 5-11 year follow-up. Similarly, Lombardi *et al*[42] demonstrated very similar results for a metal on metal bearing (manufactured by Biomet) compared to metal on polyethylene at 3 years. Jacobs *et al*[43] also recently published a comparative study between metal on metal (manufactured by DePuy) and metal on polyethylene, again with very similar results between the two groups albeit with relatively short (3-6 year) follow-up.

More compellingly, Naudie *et al*[44] studied a database of total hip replacements in Switzerland and compared two matched groups of patients. The patients were matched for gender, age at surgery (within 5 years), diagnosis, hospital where the surgery was performed, date of surgery (within 5 years), and length of follow-up (within 1 year). Patients were also matched for type of femoral stem (system and component),

and by acetabular component design. The metal on metal bearings demonstrated a lower risk of aseptic stem and/or cup loosening than the metal on polyethylene bearings, however this was not statistically significant.

These studies are hugely encouraging in that it would appear that the short term failures which plagued the first generation metal on metal hip replacements have now been eradicated by more modern designs. Modern prostheses benefit from both improved design and improved manufacturing. Improved design in that there is an increased range of motion to impingement with modern modular designs (as compared to the large-necked Thompson stem used for the McKee-Farrar THR). Improved manufacturing in that equatorial contact is no longer possible due to more accurate machining and, perhaps more importantly, improved measurement technology which ensures all components are in the desired size range with appropriate sphericity deviation and roughnesses. This also negates the need for manufacturing in matched pairs. Further, there have been no reported complications uniquely associated with the metal on metal bearings with the exception of a very low incidence of hypersensitivity. Several long term studies have shown no ill effects associated with ion release from these devices.

Conclusions

- There is undoubtedly higher metal ion release from metal on metal bearings than from other hip bearings.
- For large diameter bearings, it appears that the blood serum ion levels increase sharply during the first 12-18 months and then decrease over time and may not, in fact, be a long term problem.
- For conventional 28mm metal-on-metal bearings, the levels of cobalt and chromium appear to remain more constant in the short term.
- Hypersensitivity can and does occur but is extremely infrequent and is the subject of much research at present.
- There is no evidence to support a hypothesis of detrimental health effects due to ion release from these devices.
- Modern metal on metal hip replacements do not appear to suffer from unexpected early failures which characterised the first generation devices due to their improved design and manufacturing technology.

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Analysis of 1st Generation Metal on Metal Hip Replacements

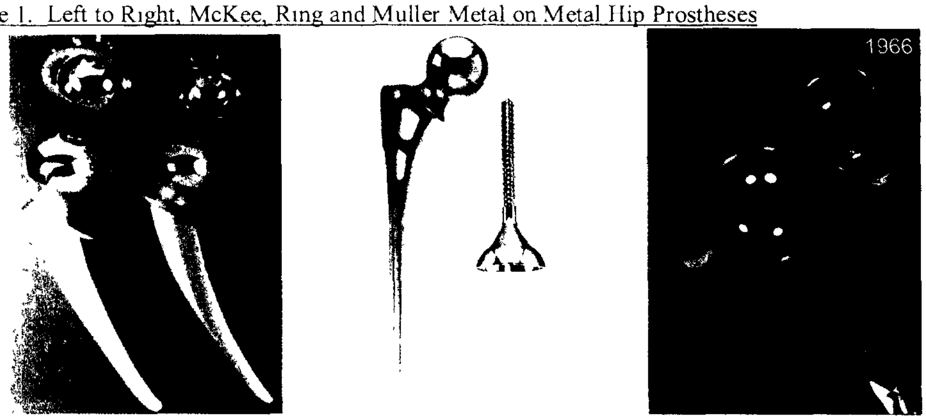
Information in Support of Downclassification

J Nevelős PhD based on a report by M Tuke
July 05

Introduction

As part of the various analyses carried out in support of the petition to downclassify metal on metal hips, several first generation devices were analysed geometrically in order to improve our understanding of these devices. It is well known (and discussed in detail in this petition) that 1st generation metal on metal hips had a significantly higher failure rate than would be acceptable today, however, there are many 1st generation metal on metal hips which have survived with remarkably little wear into the third decade of implantation. This report analyses three Ring type hips which have not been implanted, 4 retrieved McKee Farrar type hips and one Muller type. These designs are shown below.

Figure 1. Left to Right, McKee, Ring and Muller Metal on Metal Hip Prostheses



1. Non-Implanted Ring Prostheses

Materials and Methods

These prostheses were measured using standard three dimensional co-ordinate measuring techniques at the University of Leeds, Finsbury Instruments Ltd, and Adept Inspection ltd. Measurements were primarily of the form of the bearings to determine the initial clearances of the bearings. The results are shown in Table 1. Surface finish measurements were also taken at the University of Leeds which are shown in Table 2.

Results

Table 1. Measurements of Ring Metal on Metal Hips

Hip	Ave Head Diameter (mm)	Ave Cup Diameter (mm)	**Ave Diametral Clearance (µm)**	Approx Error (µm)
No. 1	39.64	40.44	**799**	+/- 23
No. 2	41.09	41.26	**175**	+/-80
No. 3	40.97	41.17	**194**	+/- 5

Table 2. Surface roughness measurements for the heads

Hip	Position	Surface roughness parameter (microns)			
		R_a	R_p	R_v	R_{sk}
No.1	Pole 1	0.0732	0.1493	0.1267	-1.1939
	Pole 2				
	Circumference	0.0230	0.0710	0.0602	0.2158
No. 2	Pole 1	0.0038	0.0120	0.0205	-0.7364
	Pole 2	0.0391	0.1172	0.0809	0.7516
	Circumference	0.0265	0.1010	0.0623	0.3717
No. 3	Pole 1	0.0467	0.1288	0.1211	0.0823
	Pole 2	0.0239	0.0964	0.1375	-0.0434
	Circumference	0.0248	0.0616	0.1239	-1.5405

Discussion

The measurements were somewhat complicated by the fact that the cups has small 'dimples' at the poles (slight flattening). The measurement profiles were adjusted to avoid these areas and several measurements were taken as is common practive. There are therefore larger errors associated with some of the measurements. Hip No 1 was not a matched pair unlike hips Nos. 2 and 3. It is interesting to note that Hips 2 and 3 have diametrical clearances which would be acceptable today and probably within the tolerances of most currently manufacturers devices. Hip No.1 however has a very large clearance, much larger than anything currently on the market and, if implanted, this hip would be likely to produce a large amount of wear before it 'bedded in.' The general form of these hips though would not be accepted today as modern devices are manufactured as perfect spheres to within 10μm. It is unclear as to whether the polar dimples were design features to improve elasto-hydrodynamic lubrication or were a manufacturing limitation.

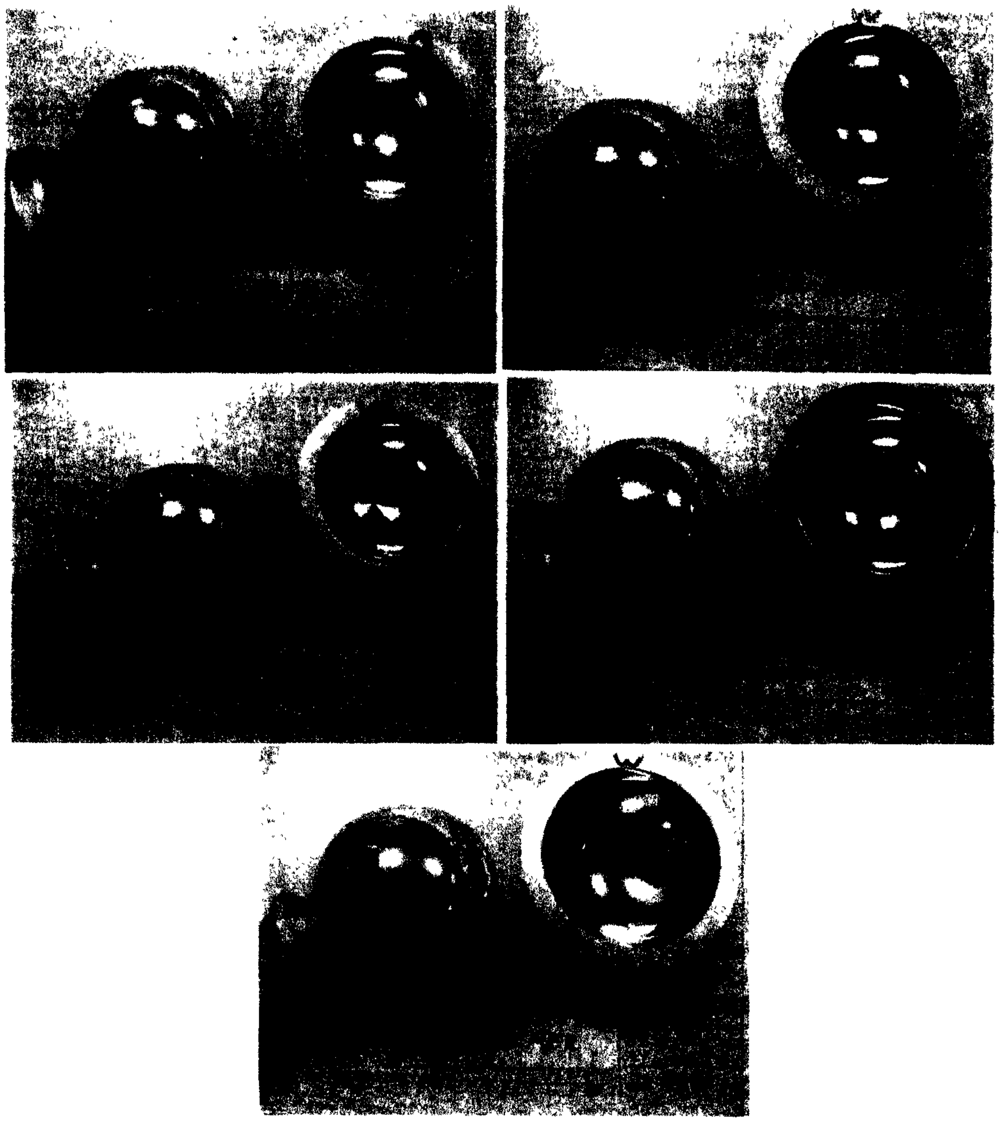
The surface data is of limited use as these implants have obviously been handled over the years and are not 'as manufactured' in terms of surface finish. The surface scratching is not of sufficient magnitude however to affect the overall dimensions of the bearings although there is a significant error on the measurements taken.

Overall this very small sample of three first generation hips did fit with clinical observations in that two of the three have acceptable bearings in terms of geometry and the third does not although admittedly it may not have been sold as an acceptable implant pair.

2. Retrieved Prostheses

Materials and Methods

Each of the retrieved components were analysed macoscopically and photographed at Finsbury Instruments ltd. Worn areas were marked in felt tip pen. The heads were measured for diameter around their equatorial regions by micrometer and laser to attempt to determine their diameters prior to implantation. The heads were then measured for roundness, again in the equatorial region. The cups were treated similarly and measured for internal geometry by a proprietary interative method which determines the minimal condition of the geometry. The retrieved implants are shown below. Three of the pairs are McKees from a single manufacturer as the trade name 'Vitallium' is marked on them. The fourth McKee (Rohschneider) may be from a different manufacturer) The final retrieval (Schaefer) is a Muller type prosthesis which was designed to have three UHMWPE spacers in the socket. These are missing and it appears that cement has extruded through the holes left by the UHMWPE bearings. There is no information as to whether this was done deliberately. The implant did survive *in vivo* for 11 years however.



Results

The results of the measurements are shown in Table 4. There are inherent inaccuracies in measuring these retrievals as wear has taken place and also these retrievals have all been handed since being retrieved. Some observations can be made about the wear patterns though. These are recorded in Table 3.

Hip	Comments
Wickert	Typical wear pattern with wear on superior quadrant of the femoral head. Dimple in cup prevents accurate cup measurement.
Planer	Possibly a matched pair prior to implantation with low initial clearance. Some evidence of 'cone clutch' wear pattern due to dimple (flattening) on both the cup and the head and therefore not a polar bearing.
Farmer	Similar to Planer, large head dimple prevented polar contact and therefore a cone clutch effect is seen.
Rohschneider	Large contact area but overall low wear penetration. Polar bearing.
Schaefer	Holes in articulating surface of the cup. Large wear area, difficult to analyse.

Table 3. Measurements of Retrieved 1st Generation Metal on Metal Hips

Patient	Time in vivo	Sex	Reason for retrieval	Implant Type	Head Equatorial Diameter (mm)	Head Roundness Polar (μm)	Head Linear Wear (μm)	Estimated Original Diametral Clearance (μı
Wickert	20y	?	Unknown	McKee	34.52 - 34 66	28	32	150
Planer	7y	F	Aseptic loosening	McKee	34 87 - 34.66	21	22	40
Farmer	20y	F	Autopsy but cup loose and acetabular #	McKee	34.91	65	~10	120
Rohschneider	1y	F	Infection	McKee*	34.93	2.5	2	120
Schaefer	11y	?	Aseptic cup loosening	Muller	36 85 - 36.86	27	~20	260

*Different Manufacturer to the other three McKees

Discussion

These retrievals are interesting in that there are several wear patterns. Two of the retrievals show evidence of a 'cone clutch' or equatorial bearing phenomenon. This occurred not because the head was bigger than the cup but rather that the head had a dimple (flattening) on the pole which prevented polar contact. Again, whether this was an intentional design feature is not known. Regardless of this these two implants survived 7 and 20 years *in vivo* respectively therefore these wear patterns presumably did not immediately lead to high friction and failure. Rohschneider is the only short term failure and this has been attributed to infection and not mechanical failure so it could be concluded that none of these five retrievals were retrieved due to early bearing failure. The articulation of the Farmer retrieval in particular is interesting in that it was an equatorial bearing but it still lasted *in vivo* for 20 years. Regardless of this (and due to the lack of any clinical information, for example we do not know if the hip was stiff and/or painful and we don't know if the patient remained active) we can state that this bearing is not optimal and not acceptable by modern standards.

Conclusions

These two sets of implants do not come with enough information to make firm conclusions about all 1st generation implants however even this small samples does highlight the variability of manufacturing and tolerancing and one can easily see how this factors might have impacted the observed clinical results of some early failures and also some excellent clinical outcomes for over 30 years. This data should be viewed as being supportive of modern metal on metal hips which benefit not only from improved manufacturing but also very accurate inspection which has removed any variability from the bearing design.