Lynne C. Jones · A. Seth Greenwald
Warren O. Haggard *Editors*

Metal-on-Metal Bearings

A Clinical Practicum

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Preface

Over a million metal-on-metal hip prostheses have been implanted since 1996, according to the Hip Society [1]. Controversy arose with reports of adverse tissue reactions and increased rates of revision associated with some of the implant designs during the 2000s. Today (2013), while many orthopaedists have discontinued using metal-on-metal implants, others continue to implant prostheses with this hard-on-hard bearing. This book will review the current understanding of the history and rationale for the development of metal-on-metal hips, the clinical experience, the basic science, and the future. As an outgrowth of several workshops on the topic, this book represents a collaborative effort between members of the Orthopaedic Research Society, the American Academy of Orthopaedic Surgeons (Biological Implants Committee, Biomedical Engineering Committee, and the Orthopaedic Device Forum), and the Society For Biomaterials.

The book is divided into five sections. Part one provides a historical review of metal-on-metal implants and poses the questions that have been raised concerning their use. The second part focuses on the clinical experience with modern metal-on-metal implants. It discusses the results of registries and outcome studies as well as the significance of testing patients for metal ion levels and hypersensitivity. Part three explores the biological response to metal-on-metal implants. Beginning with a discussion of the basic tenets of wound healing, inflammation, and immune responses, the implications of the adverse reactions seen around metal-on-metal implants are then analyzed by experts in the field. Part four discusses the possible contribution of the materials used in the manufacture of these implants, with special emphasis on wear mechanisms and tribocorrosion. The closing chapter of the book explores future directions.

We hope that this book will become a reference source for orthopaedic residents and fellows, orthopaedists, academics studying joint arthroplasty, and their colleagues in industry.

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Part I
Introduction

Chapter 1
Overview of Metal-on-Metal Implants

Lynne C. Jones, Warren O. Haggard and A. Seth Greenwald

Since the introduction of orthopaedic devices, the selection of biomaterials has played a primary role in the ultimate success of the implant. This is especially true for the materials used for the articulating surfaces of joint replacement prostheses. A number of different materials have been used for articulating surfaces with differing eventual outcomes (Table 1.1). While metal-on-polyethylene articulations have been the most widely used in the modern era of joint replacement, hard-on-hard bearings have also provided an alternative bearing surface. Metal-on-metal (MoM) was first introduced in the 1950s for total hip replacement by Drs. McKee and Farrar (Table 1.2). Their early results were unsatisfactory with two of three being removed at one year for loosening (both stainless steel alloy) and the third removed (cobalt-chromium alloy) for fracture of the femoral component [1]. After further modification of the design of the prosthesis, the outcomes improved and longer implantation times were achieved. The reported outcome for the McKee-Farrar total hip replacement has been as high as 77 % survivorship at 20 years [2], and case reports for the Ring [3] and Sivash [4] have also indicated the potential for long-term survival. The results for these early MoM designs, however, were diminished by a high rate of loosening of the

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Table 1.1 Types of bearing surfaces

1881	Gluck [45]	Ivory on ivory
1938	Wiles [40, 42–44]	Stainless steel ball on stainless steel socket
1951	George K. McKee and J. Watson-Farrar [40]	Stainless steel on stainless steel socket
1953	G.K. McKee and J. Watson-Farrar [1]	Cast CoCr on cast Co-Cr
1953	Haboush [44]	Double cup
1958	Charnley [42, 43, 45]	CoCr on polytetrafluorothylene
1959	Sivash [5, 40]	CoCr alloy femoral head and acetabular liner with titanium alloy (Ti-6Al-4V0) acetabular shell and femoral stem
1960	Charnley [42, 44]	PTFE on PTFE double cup
1960	Townley [44, 46]	Double cup arthroplasty; metal on polyurethane; metal on polyethylene
1962–1986	Charnley [41, 43, 47–49]	SS on UHMWPE (1960s); Co-Cr on UHMWPE (1960s); Ceramic head on UHMWPE (1970s)
1960s	Judet [50, 51]	Long stem femoral stem with snap-cup acetabulum; also a premounted femoral head in an UHMWPE cup
1960s	Smith [52]	CoCr; Austin-Moore prosthesis to a Gaenslen acetabular component
1964–1965	Ring [53]	CoCr on CoCr
1968	Weber-Huggler [54]	Polyoxymethylene polyacetal femoral head on metallic femur on cast Co-Cr cup (Teflon spacers)
1968	Muller [46]	Metal double cup
1963–1971	Stanmore [55]	Cast CoCr on cast CoCr
1969	Christiansen [56]	CoCr alloy on polyacetyl resin (also plastic trunnion sleeve)
1970	Exeter [57]	SS on UHMWPE
1970, 1972	Boutin [41, 43, 58, 59]	Alumina on alumina; alumina on UHMWPE; all ceramic femur
1970s	Gerard [60, 61]	Metal double cup; metal on UHMWPE double cup; metal-backed poly cup
1971	Oonishi et al. [62]	Crosslinked UHMWPE (γ-irradiated) on stainless steel monoblock stem
1973	Griss [59]	Alumina on alumina
1973	Mittelmeier [59]	Autophor; ceramic ball on ceramic socket
1975	Amstutz [63]	Total hip articular replacement using internal eccentric shells
1975	Sarmiento [64]	Titanium on UHMWPE
1977	Sedel/Ceraver [59]	Alumina on alumina
1980	Bousquet [65]	Ceramic on UHMWPE on Titanium or stainless steel (dual mobility)
1983	Amstutz [66]	Porous surface replacement (PSR) UHMWPE liner and CoCr head, then Alumina head
1984	Mallory Head [67]	Titanium alloy ball on UHMWPE
1986	Lord [59, 68]	Zirconia ceramic ball on HDP liner
1989	Several companies [69]	Ceramic on UHMWPE (US approval)
1990	DePuy Orthopaedics [70]	Metal on Hylamer (Extended Chain Recrystallized UHMWPE)

Table 1.1 (continued)

1990s	Wagner [66]	CoCrMo metal-on-metal resurfacing
1990s	McMinn/Birmingham [66]	CoCrMo metal-on-metal resurfacing
1991	Weber [41, 76]	Metasul metal-on-metal
1993	Conserve® Plus [66]	CoCrMo metal-on-metal resurfacing
1998	Several companies [71]	Metal on first generation highly crosslinked UHMWPE
2003	Smith and Nephew [72]	Oxinium/zirconium on UHMWPE
2004	ASR hip [73]	CoCrMo metal-on-metal resurfacing
Late 2000s and early 2010s	Several companies [74]	Metal on second generation highly crosslinked UHMWPE
2011	DePuy [75]	Ceramic on metal

Table 1.2 Metal-on-metal articulations

I. Total hip prostheses	
Wiles	
McKee-Farrar	Down Brothers Ltd. / Hunton Engineering
Stanmore	Zimmer to 1984 / Biomet from 1984
Ring	Downs Surgical Ltd.
Müeller	
Huggler	
Sivash	U.S. Surgical / Joint Medical Products
ASR THR	DePuy
Metasul	Sulzer/Zimmer
M2a and M2a Magnum	Biomet
Pinnacle Ultimet	DePuy/J&J
S-ROM	Johnson & Johnson
Summit	DePuy/J&J
Zweymüller-Plus total hip arthroplasty system	Smith and Nephew Orthopaedics (Rotkreuz, Switzerland)
II. Hip resurfacing prostheses	
McMinn Birmingham Hip Resurfacing (BHR)	Midland Medical Technologies/Smith & Nephew Orthopaedics Ltd., Memphis, Tennessee
ConservePlus	Wright Medical Technology Inc., Arlington, Tennessee
CormetTM	Corin Ltd., Cirencester, Gloucestershire
Durom	Zimmer Inc., Warsaw, Indiana
ReCap	Biomet Orthopedics, Warsaw, Indiana
Articular Surface Replacement (ASR)	Depuy International Ltd., Leeds, Yorkshire
ACCIS	Van Straten Medical, Netherlands
BS	ESKA Implants, Lübeck, Germany
ADEPT	Finsbury Orthopaedics Ltd., Leatherhead, UK
ICON	IO International Orthopaedics Holding, Geisinger, Germany
MRS Modular	Lima LTO, Italy
MIHR International	Comis Orthopaedics Ltd., UK
MITCH	Finsbury for Stryker
ROMAX	Medacta Australia
DynaMoM	Tornier, Netherlands

components—primarily a consequence of imprecise manufacturing tolerances and implant design [5]. However, one striking feature of retrieved implants from this generation of MoM implants was that there was little evidence of significant wear [5–7].

In the wake of the numerous reports documenting the adverse tissue response to polyethylene wear debris for metal-on-polyethylene prostheses in the 1980s and 1990s, alternative bearing surfaces were again explored. Metal-on-metal articulating surfaces were reintroduced in the early 2000s for both total hip and resurfacing arthroplasty procedures [8, 9]. The rationale for MoM bearings included (1) improved metallurgy and fabrication with the ability to manufacture components with controlled surface roughness, sphericity, inclusions, and clearances, (2) improved implant designs, (3) improved surgical technique, (4) substantially lower wear rates than seen for metal-on-polyethylene, and (5) the availability of larger-diameter femoral head sizes [10, 11]. In 2009, Bozic et al. estimated that 35 % of all total hip replacements incorporated MoM bearings [12]. Also, increased numbers of metal-on-metal resurfacing hip devices were seen in the 2000s, peaking in 2006–2007 as outlined in a study by Tucker et al. [13].

Initial reports of short-to-midterm outcomes for the current generation of MoM total hip and resurfacing hip surgeries were favorable [14–16]. However, more ominous findings on clinical outcomes were slowly appearing in the medical literature. In the early 2000's there were several reports of elevated serum metal ion levels in patients with MoM implants [17–19]. In 2003, Jacobs and colleagues warned that there was evidence of elevated serum and urine cobalt and chromium in patients with MoM bearings and that vigilance was required in following these patients for evidence of delayed type IV hypersensitivity reactions and, potentially, carcinogenic effects [20]. The first awareness of increased rates of revision was based on the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR) in 2008 [21]. At about the same time, reports of inflammatory soft tissue masses associated with MoM implants began to surface [22–24]. Increasing awareness was intensified by increasing numbers of publications in the medical literature as well as by increasing awareness of the public fueled by implant recalls and numerous newspaper articles.

A number of regulatory and orthopaedic societies have weighed in on the subject of MoM total and resurfacing hip implants. In 2010, the British Orthopaedic Association issued a medical device alert regarding MoM hip replacement and hip resurfacing arthroplasty, the incidence of serious soft tissue reactions, and elevated levels of cobalt and chromium ions [25]. In 2011, the American Society for Testing and Materials (ASTM) International held a workshop on MoM to discuss the current state of MoM hip replacement and the need for better standards [9]. In the same year, the American Academy of Orthopaedic Surgeons published a systematic review of the published literature regarding the use of "modern" MoM hip implants as a technology overview of the prevalence of adverse responses, the revision rates, and the likely risk factors [26]. The Food and Drug Administration (FDA) has also issued their report on the "Concerns about Metal-on-Metal Hip Implants" [27], which followed

in a call for premarket approval (PMA) applications to appreciate the outcomes of contemporary MoM hip devices. However, a European multidisciplinary study group of 21 experts concluded that "Despite various national recommendations, efforts to achieve international harmonization of specific evidence-based recommendations for best practice are still lacking" [28].

It is apparent that more questions than answers have been raised by the scientific community surrounding MoM implants. However, as the use of MoM prostheses is ongoing, the need for answers is immediate and not just a philosophical debate. There are two major issues that the orthopaedic surgeon must evaluate: (1) Are MoM bearings a viable alternative to other articulating bearings and (2) what is the best action plan for taking care of patients with existing MoM implants? On the one hand, the answers to these questions need to be based on an understanding of the basic principles of biology, materials science, and biomechanics. On the other hand, the answers need to be based on the clinical evidence.

As discussed in this practicum, the nature of articulating orthopaedic implants is that they eventually wear. How much depends on the materials in the bearing couple, the demands placed on the joint, and the implant design and implantation. Modular connections introduce additional sources for debris and metal ion release including head–neck, stem–neck, and midstem tapers [29–33] which have the potential to evoke systemic and local tissue responses [33, 34]. While wear from metal-on-polyethylene and ceramic-based implants appear to evoke a nonspecific, nonantigenic response, metal wear and the associated metal ions have the capacity to incite both nonspecific and specific immune responses [35–38]. The potential mechanisms involved are introduced by Goodman (Chap. 2) but are a recurring theme throughout this practicum.

A discussion of the clinical experience of MoM hip arthroplasty implants is considered from several points of view including an evaluation of the results from established implant registries, reports from clinical series, as well as examination of the tissues interfacing with compromised implants. The eventual outcome of MoM arthroplasty procedures, as discussed by Mont and Pivec (Chap. 3), may range from stable interfaces to severe osteolysis requiring revision. The higher failure rates experienced with some designs of MoM implants at earlier time points than reported for metal-on-polyethylene implants is a major concern. But what is happening at the implant–tissue interface? Are the cells in the periprosthetic tissues mostly macrophages or lymphocytes? Are the cells activated? Are they responding to metal particles (nanoparticles and microparticles) and/or metal ions? A review of the pathology can give us some understanding of what is happening at this microscopic level, as described by Grammatopoulos et al. (Chap. 4) and Bauer (Chap. 9). Is there a threshold, as suggested by Langton (Chap. 5)? Are low levels of metal ions "reassuring" or an enigma? Who is at risk? There has been considerable discussion about the type of patient but evidence shows that adverse tissue responses are not limited to one patient cohort. Is there a way to objectively measure whether a patient is at risk for an adverse tissue response and, if so, what laboratory tests should be obtained? We can measure serum levels of metal ions, but this measure in and of itself does not tell us how an individual patient will respond. The debate has surrounded

the use of skin patch testing versus lymphocyte transformation testing; an excellent description of the strengths and weaknesses of these tests have been provided by Hallab and Wooley (Chap. 6) and Thomas et al. (Chap. 10).

In trying to comprehend the characteristics of what has been labeled as a pseudotumour, it is important for us to understand the biological principles of wound healing, acute and chronic inflammation, and the immune response. Dee et al. [39] stated:

> A crucial concept to understand about the tissue–biomaterial interface is that a lot of things happen there! The environment inside the body is chemically, electrically, and mechanically active, and the interface between an implanted material and the body is the location of a variety of dynamic biochemical processes and reactions.

This understanding is even truer for the microenvironment surrounding wear debris. Laboratory and clinical studies have reported differing responses to different types of materials and sizes of debris. As discussed by Wooley and Hallab (Chap. 7), while a biological threshold is likely to play a significant role as a trigger to an adverse tissue response, the length of continuous exposure is also likely to play a role. While we are debating over whether the findings of pseudotumors are Type IV hypersensitivity reactions or not, Cooper and Jacobs (Chap. 8) suggest that more than one instigator may be involved ranging from inorganic metal salts and oxides to the presence of metal wear nanoparticles. In fact, these different metal-based stimuli are likely to be present simultaneously as time of implantation and use increase creating an unstoppable chain of reactions. However, Bauer encourages us to recognize that there is a diversity of adverse tissue responses. That these differences may be related to differences between the source of the stimulus as well as patient-related factors is a reasonable premise.

Is there a future for MoM implants? It is important to recognize that there are several currently implanted MoM prostheses that have successful outcomes with mid- to long-term follow-up. In determining the factors that differentiate between success and failure, Pourzal, Urban, and Wimmer (Chap. 11) note that we need to evaluate the implant itself: the materials, the design, and the kinematics of the resurfaced joint. Metal-on-metal implants are usually made of alloy of cobalt and chromium, and the presence of higher yields of carbides may influence the behavior of the material. As discussed by Thomas et al. (Chap. 10), a number of design and surgical factors may contribute to increased wear and corrosion including whether there is an increased risk of impingement and the use of modular implants. A better understanding of tribology and tribocorrosion is also very important in future evaluations and assessments for all types of articulating surfaces involving metal–metal interfaces.

The answers to the questions raised in the ensuing chapters of the practicum should be based on the evidence—which would require sifting through hundreds of articles, white papers, and government documents. The goal of this book is to provide the reader with an overview of the issues surrounding the use of MoM hip prostheses from the experts in the field. However, the reader is strongly encouraged to investigate further.

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Chapter 2
Bearing Surfaces for Joint Replacement: New Materials or New Problems

Stuart Goodman

Total joint replacement (TJR) is one of the greatest technological advances in all of surgery. Hip, knee, and shoulder replacements, as well as reconstruction of smaller joints with artificial materials are currently performed worldwide. These procedures decrease pain and improve function in a cost-effective manner, and thereby improve the quality of life for millions of patients with end-stage arthritis.

Initially, most modern TJRs consisted of a bearing couple composed of a metallic alloy that articulated with conventional medical grade polyethylene [1]. This combination of materials functioned satisfactorily for many years in low demand, elderly patients for whom TJRs were originally designed. However, as joint replacement procedures were extended to younger more active higher-demand patients, wear of the polyethylene and the subsequent adverse biological reaction to wear byproducts became a serious concern [2].

Wear of the bearing materials of a TJR is a function of use, not time in vivo [3]. Higher-demand patients engage in greater numbers of gait cycles per day, and often participate in higher-impact sporting activities that increase wear [4]. Polyethylene wear particles generated at the articulation are pumped and distributed throughout the "effective joint space", producing in some cases chronic synovitis, progressive bone loss (periprosthetic osteolysis), implant loosening and pathologic fracture [5]. Subsequent surgical reconstruction of loose TJRs with extensive periprosthetic bone loss is challenging; these surgical procedures are long and costly and have a higher complication rate and a poorer outcome compared to primary procedures [2]. These facts have stimulated intense research to improve the tribological characteristics of current materials, as well as develop newer more wear resistant bearing couples that potentially could last a lifetime [6]. Although this goal has not yet been realized, significant improvements in implant materials have been achieved in the last two decades. At the same time, unexpected obstacles have surfaced which have led, in some cases, to earlier revision surgery than with conventional materials.

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The Inflammatory Reaction to Wear Debris

Wear particles are generated at all artificial joint articulations. These particles are largely in the micron and submicron range, with metallic particles being amongst the smallest [7–9]. Wear particles of polymethylmethacrylate (PMMA), polyethylene (PE) and ceramics evoke a nonspecific, non-antigenic chronic inflammatory and foreign body reaction [10]. The cellular components of this reaction commonly include the monocyte/macrophage cell lineage (macrophages, foreign body giant cells and osteoclasts), activated fibroblasts, with occasional polymorphonuclear leukocytes (PMNs) and lymphocytes [11–13]. Larger wear particles of metals such as stainless steel, cobalt chrome alloy and titanium alloy incite a similar chronic inflammatory reaction; however, recent evidence has demonstrated that metal byproducts may also produce a Type IV allergic reaction in some situations (see below) [14].

Macrophages and other cells phagocytize particles less than about 10 microns in diameter, as part of the innate immune response to foreign materials [2, 7, 8, 13, 15]. The wear debris is non-digestible and activates the cells to produce and release pro-inflammatory cytokines, chemokines, prostanoids, reactive oxygen species and other factors that, in the end, stimulate osteoclasts to degrade bone [15–17]. At the same time, homeostatic mechanisms are initiated that induce local bone formation [13, 18]. However, with ongoing production of wear debris, the balance between bone destruction and bone formation favours the former, leading to periprosthetic osteolysis, and potentially, implant loosening and fracture [18, 19]. Because of the cyclic nature of walking which induces high intra-articular pressures, the particles, cells and inflammatory factors are pumped and distributed around the prosthesis and insinuate into the adjacent cancellous bone along the bone–implant interface [20]. From this pumping and distribution, osteolysis can be seen adjacent to and remotely from the prosthesis bearing couple. Increased local fluid pressure also induces bone destruction [21]. The cells that phagocytize particles eventually die, liberating the particulate debris that continues to perpetuate the inflammatory cycle. Furthermore, recent in vivo studies have shown that wear particles induce a systemic biological response, rather than only a local response [22, 23]. Through the action of chemotactic cytokines or chemokines, inflammatory and reparative cells are mobilized to the site of particle generation to participate in the inflammatory cascade, attempt to contain this adverse reaction, and restore normal tissue architecture [22–27].

Although biological approaches are currently being explored to improve the osseointegration of implants (to provide a more robust bone–implant interface) and to mitigate wear particle induced inflammation, perhaps a more direct approach is to develop more wear resistant materials. In essence this amounts providing bearing couples that generate fewer wear particles, with conceivably more benign biological physico-chemical properties, which will not perturb local tissue homeostasis. This goal would aim to provide a “permanent” joint replacement that would allow full activities (including impact loading) for the duration of the patient’s life.

New Polyethylenes

As stated above, metal-on-conventional ultra high molecular weight polyethylene has been the traditional bearing surface for many decades. This material has performed well in the very elderly, more sedentary population. However, in more active younger individuals with greater numbers of gait cycles per year, more wear particles are produced [3]. In general, polyethylene linear wear rates of less than 0.1 mm per year produce little osteolysis compared with higher wear rates [28]. Increased wear is produced by chain scission and oxidation of the linearly arranged polyethylene molecules. Recent attempts to improve the wear characteristics of polyethylene have included: altering the crystallinity of polyethylene, irradiating and packaging the product in an inert (non-oxygen containing) environment, irradiating and heating (above the melting point) and/or annealing the polyethylene to induce a more highly cross-linked end product that contains fewer free radicals, sequential irradiating and annealing protocols below the melting point of polyethylene, and adding surface coatings or free radical scavengers [29–31]. Although most of these new processes have shown highly encouraging early and intermediate clinical results after more than one decade of use, no long-term (20 + year) clinical outcomes have been reported [32]. Cross-linked polyethylene (XLPE) has less optimal mechanical properties (including toughness, ductility and resistance to fatigue) compared to conventional polyethylene [33–35]. Issues related to the use of larger femoral heads (to prevent dislocation) that articulate with thinner polyethylene acetabular liners have lead to reports of polyethylene rim fractures, necessitating revision surgery [36, 37]. This has been seen more commonly in implants with suboptimal positioning (for example, an excessively abducted or anteverted acetabular cup). Although in vitro studies have suggested potentially higher adverse biological reactions to wear particles from cross-linked polyethylene, compared to conventional polyethylene, the numbers of particles generated are decreased with the XLPE material as to almost negate this point [38–40]. However, not all XLPEs are exactly alike. The irradiation protocols, processing, packaging and other variables are different for each manufacturer [32]. Patients with XLPE components are still not encouraged to engage in impact loading activities that could damage the articular surface.

Ceramic Bearings

The use of ceramic-on-ceramic (CoC) bearings was popularized in France, Japan and Korea, but has been less popular in the United States. These bearings are biocompatible, display low friction, high-wear resistance and produce few wear particles with normal usage [41]. Intermediate term series have reported very encouraging results [42, 43]. The problem of catastrophic fracture of ceramic femoral heads in total hip replacement has largely been avoided with newer ceramics with smaller grain sizes. However, some new unanticipated problems have come to light with CoC bearings [44, 45]. Modular acetabular cups may be difficult to assemble, may seat

incompletely, or dissociate from their metal backing. Third body interposition (with soft tissue, bone spicules, etc.) between modular components may be an issue in assembly. Chipping of the liner may also occur at surgery or with later impingement. Edge loading with striped wear may take place due to increased range of motion and cyclic micro-separation during gait, especially if the components are in suboptimal position [41, 44]. Troublesome and embarrassing audible squeaking has been noted with some implant designs. In addition, these implants are generally more expensive than metal-on-polyethylene (MoP) articulations. Nonetheless, CoC bearings facilitate the use of larger femoral heads and generally allow more normal activities, even high-impact sports according to surgeons who utilize them [43].

Metal-on-Metal (MoM) Bearings

MoM bearings were recently re-introduced for several reasons, including the high wear rates and high incidence of osteolysis with metal-on-conventional polyethylene bearings in younger patients, and for resurfacing arthroplasty [46]. MoM bearings depend on a high level of congruence of the articulating metallic surfaces to encourage fluid film lubrication [47]. This results in extremely low wear rates [41, 48]. The head sizes can be larger than with a MoP bearing, increasing the range of motion and overall stability of the joint. These points lead to a resurgence of MoM bearing surfaces, which at one point constituted about 25 % or more of the hip replacement market in the USA. The early and mid-term results for some MoM total hip and resurfacing implants were very encouraging [49]. However, the enthusiasm for this bearing couple has waned somewhat because of issues related to pain and adverse tissue reactions with some implants [48]. Indeed several suboptimal implant designs with unacceptably high failure rates have been withdrawn from the marketplace [50, 51].

In general, patients with MoM total hip replacements have a higher incidence of adverse tissue reactions compared with those with MoP or CoC bearings. Some MoM failures are the result of a type IV hypersensitivity reaction to metal particles and their byproducts [41, 47]. The clinical presentation may vary from a diffusely painful joint with chronic synovitis and no other abnormal radiographic features to loosening, osteolysis or pseudotumor formation. Registry data from several countries have shown a higher revision rate for MoM bearing THRs [48, 52, 53]. Larger head sizes (> 28 mm) appear to increase these adverse events compared to smaller head sizes.

Willert and colleagues published a seminal study on adverse tissue reactions to MoM bearings and implicated a hypersensitivity reaction to metallic byproducts [14]. They noted prominent perivascular lymphocytic cuffing in the periprosthetic tissues and implicated immune processes for the adverse clinical outcomes in some patients. Patients with high wear rates of MoM hip implants, especially those with suboptimal alignment leading to edge loading, may have increased metal ion levels of cobalt and chromium in the blood. In vitro and in vivo studies have demonstrated that metal

particulates and their byproducts may be associated with cytotoxicity, DNA damage (DNA-strand breaks, inhibition of DNA repair, chromosomal aberrations, etc.), metal hypersensitivity reactions and pseudotumors [47, 54]. Metal particles are about 30–200 nm in size; ionic complexes may form due to corrosion and other processes that degrade the alloys. The numbers of these smaller particles are often 2–3 orders of magnitude greater than with MoP articulations. These small metallic particles are small enough to cross the placenta. Although some hematopoietic abnormalities have been noted with MoM bearings, the incidence of different cancers in patients with MoM bearing surfaces does not appear to be higher compared to conventional MoP bearing surfaces [55].

In the last several years, the number of new MoM resurfacing arthroplasties has decreased dramatically, especially in younger women with smaller implant sizes [56]. These higher-risk patients are particularly susceptible to adverse immunological events due to wear byproducts from MoM implants [47]. Resurfacing arthroplasty is reported to have a much higher success rate in younger males with good bone stock and little deformity.

Other Bearing Couples

Other novel, so-called "hard-on-hard" bearing couples (such as ceramic-on-metal etc.) have recently been introduced to avoid the metallic byproduct issue altogether [46]. Longer-term studies are needed to determine their importance as a practical articulation for hip replacement.

Summary

As the general population continues to age, and high demands are placed on joint replacements to function for prolonged periods of time, issues related to implant materials become more prominent. Thorough preclinical assessment of newly introduced materials must be rigorous to avoid some of the pitfalls noted during the last one to two decades. Although advances have been made, the long-lasting, high-performance joint replacement that will function normally in vivo is still elusive.

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Part II
Clinical

Chapter 3
Outcome Studies for Metal-on-Metal Bearings: What Evidence-Based Medicine Tells Us

Michael A. Mont and Robert Pivec

Introduction

Metal-on-metal (MoM) total hip arthroplasty (THA) has a long record of use in the orthopedic community beginning with the McKee–Farrar [1] and Ring [2, 3] metal bearing designs. These articulations provide the theoretical benefit of less linear wear, large-diameter femoral heads, and increased stability [4, 5]. Some early studies [6, 7] demonstrated similar implant survivorship, with a 20-year implant survivorship of Charnley stems using cemented polyethylene acetabular cups being 73 % compared to 77 % for the McKee–Farrar prosthesis (Table 3.1). However, the desire to further reduce wear compared to polyethylene and improve stability led to an impetus to design second-generation MoM components in the late 1990s.

MoM bearings became increasing popular in the early 2000s, and were seen as a potentially ideal bearing option for the young, active patient who was more likely to place increased demand on their joint [8, 9]. Concerns with dislocation, wear, aseptic loosening, and osteolysis with early-generation MoP bearings led some surgeons to seek alternative bearing surfaces in patients whose life expectancy was likely to be longer than the expected longevity of the MoP bearing couple [10]. However, clinical results demonstrated higher revision rates, concerns with higher frictional coefficients and torque, and metal hypersensitivity, which have tempered their use. An overview of these results can be seen in Tables 3.2, 3.3 and 3.4. Overall, the mean implant survivorship at less than mean 5-year follow-up, based on the current literature, is 95 %. This is in line with recent national joint registry data from the United Kingdom and Australia which demonstrate similar revision rates [11–13].

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Table 3.1 Results: First-generation MoM THA

Study	Device	Number of patients (Hips)	Age (Years)	Mean follow-up (Years)	Osteolysis (%)	Revisions (%)	Survival (%)
McKee and Farrar (JBJS Br, 1966)	McKee–Farrar	50 (50)	–	3.0	–	4	96
Dandy et al. (JBJS Br, 1975)	McKee–Farrar	– (739)	–	5.0	–	7	93
August et al. (JBJS Br,1986)	McKee–Farrar	808 (808)	62	20.0	–	8	92
Higuchi et al. (Arch Orthop Trauma Surg, 1997	McKee–Farrar	38 (38)	57	11.3	–	29	71
Gerritsma-Bleeker et al. (JBJS Br, 2000)	Stanmore	135 (146)	70	22.0	–	15	85
Brown et al. (CORR, 2002)	McKee–Farrar	101 (123)	61	28.0	–	26	74
Total		*1,871* (*1,904*)	*62*	*14.9*	–	*15*	*85*

Table 3.2 Results: Second-generation MoM THA (Metasul™; < 10 years)

Study	Device	Number of patients (Hips)	Age (Years)	Mean follow-up (Years)	Osteolysis (%)	Revisions (%)	Survival (%)
Weber et al. (CORR, 1996)	Metasul	110 (110)	59	3.5	–	5	96
Wagner et al. (CORR, 1996)	Metasul	70 (70)	50	2.8	0	0	100
Hilton et al. (CORR, 1996)	Metasul	74 (74)	71	2.2	0	1	99
Randle and Gordiev (Aust NZ JS, 1997)	Metasul	57 (57)	63	– (0.4–2.6)	0	0	100
Dorr et al. (JBJS Am, 2000)	Metasul	56 (56)	70	5.2	0	5	95
Wagner and Wagner (CORR, 2000)	Metasul	78 (78)	49	5.0	0	4	96
Lombardi et al. (J Arthroplasty, 2001)	Metasul	78 (78)	49	3.3	0	0	100
MacDonald et al. (CORR, 2003)	Metasul	22 (22)	–	3.2	0	0	100
Brodner et al. (CORR, 2003)	Metasul	50 (50)	58	5.0	2	0	100
Delaunay (J Arthroplasty, 2004)	Metasul	89 (98)	60	6.0	1	5	95
Kim et al. (JBJS Am, 2004)	Metasul	62 (70)	37	7.0	3	4	96
Long et al. (J Arthroplasty, 2004)	Metasul	154 (161)	56	6.5	0	4	96
Migaud et al. (J Arthroplasty, 2004)	Metasul	30 (39)	40	5.7	0	0	100
Saito et al. (J Arthroplasty, 2006)	Metasul	90 (106)	58	6.4	0	1	99
Sharma et al. (Hip Int, 2007)	Metasul	– (209)	–	7.3	–	1	99
Dastane et al. (CORR, 2008)	Metasul	80 (82)	52	5.5	0	1	99
Delaunay et al. (CORR, 2008)	Metasul	73 (83)	41	7.3	0	2	98
Carr and DeSteiger (Aust NZ JS, 2008)	Metasul	125 (125)	–	– (3–9)	2	2	98
Berton et al. (JBJS Br, 2010)	Metasul	92 (100)	50	4.8	–	8	92
Long et al. (CORR, 2010)	Metasul	181 (207)	59	1.6	0	15	85
Girard et al. (JBJS Am, 2010)	Metasul	44 (47)	25	9.0	11	4	96
Vigler et al. (Bull NYUHJD, 2010)	Metasul	39 (43)	57	3.5	0	5	95
Nikolau et al. (Bull NYUHJD, 2011)	Metasul	166 (193)	50	7.0	0	7	93
Total		*1,820 (2,158)*	*53*	*5.1*	*1*	*3*	*97*

Table 3.3 Results: Second-generation MoM THA (all other implants; <10 years)

Study	Device	Number of patients (Hips)	Age (Years)	Mean follow-up (Years)	Osteolysis (%)	Revisions (%)	Survival (%)
Lombardi et al. (J Arthroplasty, 2001)	M^2a-Taper	78 (78)	49	3.3	0	0	100
MacDonald et al. (CORR, 2003)	M^2a-Taper	23 (23)	– (40–75)	3.2	0	0	100
Lombardi et al. (J Arthroplasty, 2004)	M^2a-Taper	53 (53)	50	5.7	0	0	100
Cuckler et al., (J Arthroplasty, 2004)	M^2a-Taper	78 (78)	–	5.3	–	–	–
	M^2a-38	555 (616)	–	1.1	–	–	–
Jacobs et al. (J Arthroplasty, 2004)	Ultima	95 (96)	53	3.9	0	1	99
Park et al. (JBJS Am, 2005)	Ultamet	167 (171)	55	2.3	6	1	99
Smith et al. (CORR, 2005)	M^2a-38	327 (377)	56	0.3	0	0	100
Korovessis et al. (JBJS Am, 2006)	Sikomet	194 (217)	55	6.4	6	7	94
Milosev et al. (JBJS Am, 2006)	Sikomet	591 (640)	57	7.1	3	10	100
Vassan et al. (Acta Orth, 2007)	Fitmore	94 (112)	56	7.0	0	3	94
Peters et al. (J Arthroplasty, 2008)	M^2a-Taper	160 (160)	63	4.3	0	–	–
	M^2a-38	136 (136)	56	4.3	0	–	–
	Magnum	469 (469)	54	3.0	0	–	–
Stuchin et al. (JBJS Am, 2008)	Birmingham	34 (40)	57	1.0	0	0	100
Zijlstra et al. (Orthopedics, 2009)	M^2a-Taper	102 (102)	72	5.6	–	3	97
Parmaksizoglu et al. (Hip Int, 2009) [Crowe IV DDH]	Magnum	13 (15)	46	4.1	0	7	93
Paleochorlidis et al. (Hip Int, 2009)	Sikomet	84 (99)	63	9.5	7	5	95
Engh Jr et al. (CORR, 2010)	Ultamet	126 (131)	53	5.6	2	2	98
	Ultamet	126 (131)	–	–	–	1	99
Long et al. (CORR, 2010)	Durom	181 (207)	61	1.0	0	15	85
Berton et al. (JBJS Br, 2010)	Durom	92 (100)	50	3.6	0	7	93

Table 3.3 (continued)

Study	Device	Number of patients (Hips)	Age (Years)	Mean follow-up (Years)	Osteolysis (%)	Revisions (%)	Survival (%)
Cicek et al. (Acta Belg, 2010)	Cormet	54 (59)	54	4.1	0	2	98
Donell et al. (JBJS Br, 2010)	Ultima	545 (652)	57	5.0	–	14	86
Mertl et al. (OTRS, 2010)	Durom	102 (106)	66	2.5	0	0	100
Langton et al. (J Arthroplasty, 2010)	ASR	87 (87)	67	3.4	–	6	94
Langton et al. (J Arthroplasty, 2011)	ASR	87 (87)	67	6.0	–	49	51
Bolland et al. (JBJS Br, 2011)	Birmingham & Adept	185 (199)	58	5.2	12	9	92
Latteier et al. (J Arthroplasty, 2011)	M^2a-Taper	300 (352)	57	5.0	–	4	96
	M^2a-38	577 (750)	57	5.0	–	7	93
	Magnum	335 (487)	57	5.0	–	4	96
Molli et al. (J Arthroplasty, 2011)	M^2a-Taper	304 (351)	56	6.0	–	3	97
	M^2a-38	660 (750)	58	3.9	–	5	95
	Magnum	443 (488)	58	2.6	–	3	98
Yalcin et al. (Hip Int, 2011) [Crowe I&II DDH]	Cormet	65 (75)	47	5.2	0	0	100
Total		*7,522 (8,494)*	*57*	*4.3*	*2*	*5*	*95*
Total all second-gen. implant types		*9,342 (10,652)*	*55*	*4.6*	*1*	*4*	*96*

Table 3.4 Results: Second-generation MoM THA (>10 years)

Study	Device	Number of patients (Hips)	Age (Years)	Mean follow-up (Years)	Osteolysis (%)	Revisions (%)	Survival (%)
Metasul Implant							
Grubl et al. (JOR, 2007)	Metasul	98 (106)	56	10.0	4	1	99
Eswaramoorthy et al. (JBJS Br, 2008)	Metasul	100 (104)	61	10.8	0	6	94
Park et al. (J Orth Surg, 2010)	Metasul	37 (39)	55	10.2	18	18	82
Saito et al. (Orthopedics, 2010)	Metasul	77 (90)	56	12.3	0	6	94
Dastane et al. (J Arthroplasty, 2011)	Metasul	124 (127)	64	13.0	13	9	91
Hwang et al. (J Arthroplasty, 2011)	Metasul	70 (78)	40	12.4	4	1	99
Randelli et al. (J Arthroplasty, 2011)	Metasul	111 (149)	50	13.0	0	5	95
All other implants							
Milosev et al. (JBJS Am, 2006)	Sikomet	591 (641)	57	10.0	3	8	92
Neumann et al. (J Arthroplasty, 2009)	Lubrimet	100 (100)	56	10.5	3 cup 4 stem	6	94
JIS Experience	M^2a-Taper	98 (98)	55.8	11	–	10	90
Total		*1,406* (*1,532*)	*55*	*11.7*	*5*	*6*	*94*

While all these potential complications with MoM THAs warrant concern and further evaluation, a large proportion of reports of adverse effects have been single-patient case reports or level IV studies, which may have been susceptible to selection bias [14–16]. Recently several meta-analysis and results for national arthroplasty registries have increased the awareness of the outcomes and potential complications with MoM THA [11–13, 17]. In this chapter we will provide an overview of recently reported survivorship for this bearing option divided into (1) outcomes from the literature and (2) outcomes from national joint registries.

Current Concepts with Metal-on-Metal Bearings

One of the major concerns with metal bearings is the development of local tissue reactions to metal ion debris which has been termed adverse local tissue reaction (ALTR) or adverse reaction to metal debris (ARMD) [18]. These are broad terms that encompass a host of related, but histologically distinct, findings seen at revision surgery which includes metallosis, cystic or solid masses ("pseudotumors"), and aseptic lymphocyte-dominated vasculitis-associated lesions (ALVALs) [19–22]. Although a direct correlation with elevated cobalt and chromium ion levels and ALTR has not been established, both the Hip Society [23] in the United States and the Medical and Healthcare Products Regulatory Agency (MHRA) [24] in the United Kingdom have established 7 parts per billion (ppb) as a cutoff safe level for serum cobalt and chromium ions. However, the United States Food and Drug Administration (FDA) has raised concern about the methodology that was utilized to arrive at this cutoff and has stressed that it may be inherently arbitrary in nature due to the lack of high-level studies on this topic. At this time the FDA has made no recommendation regarding what it considers to be safe serum levels for cobalt and chromium ions [25].

Adverse local tissue reactions may lead to the formation of cystic or solid masses which may have a mass-effect and compress surrounding structures [26]. The prevalence of incidentally found pseudotumors in asymptomatic patients has been reported to be as high as 32 %, while the prevalence of symptomatic lesions has been noted to be less than 1 % [27, 28]. At the time of revision surgery, extensive metallosis has also been observed to result in cellular toxicity which compromises the soft tissue sleeve of the hip joint and the abductor mechanism which may have implications for stability [29].

Cancer is one other potential concern with elevated serum cobalt or chromium ion levels since these metals have been demonstrated to be carcinogenic in animal models [30]. The release of hexavalent chromium (CrVI), which occurs in corroded cobalt–chrome alloys is a concern since this chromium form has been well established as a potential carcinogen [31–34]. However, several studies using national joint registry data have thus far found no evidence to link THA in general, or elevated serum metal ions in particular, to a risk for developing cancer [35–39]. One reason for this finding may be that CrVI is quickly reduced to CrIII within erythrocytes, which is

Table 3.5 Factors that affect serum cobalt and chromium ion concentrations following MoM THA

Prognostic factor	Correlation with serum ion levels
Femoral head diameter	Possible (diameter > 40–50 mm)
Acetabular cup inclination	Increase with steeper inclination angle
Acetabular cup anteversion	< 10 and > 20°
Activity level	No correlation
Duration of implant in situ	Increase in first 2 years; steady state after 2 years
Gender[a]	Women have higher serum metal ion levels

[a]Gender may be confounded by restricted femoral head sizing options

the form needed for normal cellular metabolic processes [37]. A recent analysis by Mäkelä et al. of data from the Finnish Cancer Registry and Finnish Arthroplasty Register demonstrated no increase in the risk for cancer compared to patients with polyethylene or ceramic bearings (incidence ratio 0.95; 95 % CI: 0.85–1.04) at 4-year follow-up [30]. Similar results were reported by Smith et al. following analysis of registry data from the United Kingdom, and particularly observed no increased risk for developing hematological or renal tract cancers which could theoretically be affected by elevated serum metal ion levels [31]. However, one point of concern is the short follow-up period (5 years) for these studies since many cancers have a relatively indolent progression and may not appear for decades.

Diagnosis and management of patients who have MoM THAs may be challenging, particularly if the patient is asymptomatic but ion levels are elevated. Recently, a collaborative effort by the Hip Society in the United States proposed a management algorithm for patients with asymptomatic and symptomatic hips which recommended close surveillance with serial serum ion levels, imaging with metal artifact reduction sequence (MARS) magnetic resonance imaging (MRI), and revision in patients who are symptomatic and have elevated ions [39].

Outcomes from the Literature

The natural history of serum cobalt and chromium metal ion levels following MoM THA has been extensively studied. Various surgeon- and patient-specific factors affect these levels, including head diameter, acetabular cup inclination, anteversion, and activity levels (Table 3.5) [40–47]. Gender has also been implicated with women being at a higher risk for having elevated serum metal ions, however this finding may be susceptible to selection bias since femoral head size correlates with gender [48].

The relationship between femoral head diameter and serum ion levels has been debated. Lavigne and colleagues observed higher serum ion levels with femoral heads greater than 50 mm, but were unable to determine if this was due to head size or somehow related to gender since only men received head sizes of this size or greater [45]. However, in a review of 104 arthroplasties, Bernstein et al. observed no correlation between serum ion levels and femoral head size [49], which is similar to what was reported by Vendittoli and colleagues in a study of 107 total hip resurfacing

arthroplasties [47]. However, resurfacing arthroplasties may not be comparable to stemmed MoM implants since the absence of sleeves or metal junctions in resurfacing prostheses eliminate potential interfaces for wear and metal debris [46]. Data from the Australian national joint arthroplasty also did not find a correlation between ion levels and head size, but a higher revision rate was observed for femoral heads greater than 40 mm [13].

Steep inclination angles have been well established as a risk factor for early failure and higher serum cobalt and chromium ions [48–50]. De Haan and colleagues demonstrated that acetabular cups implanted at angles greater than 55° were most likely to cause elevated serum ion levels, likely due to edge loading effects [50]. A similar, though non-significant, conclusion was reached by Brodner and colleagues who reported 10- to 50-fold higher cobalt and 9.5- to 30-fold higher chromium levels in patients who had cups implanted at 58–63° [49]. Similarly, acetabular cup anteversion angles outside of the "safe zone" of 20° anteversion have been shown to affect metal ion levels. Langton and colleagues, in a study of 160 patients, observed that cobalt and chromium ion levels were significantly elevated when acetabular cup anteversion was less than 10° or greater than 20° [47].

Activity levels were evaluated by Pattyn and colleagues who did not observe any correlation between activity levels and metal ion levels [41]. Similar results were reported by Heisel et al. who observed a 3 % cobalt and 0.8 % chromium serum ion level despite a 1,621 % increase in patient activity levels [42].

Temporal trends have demonstrated that serum ion levels commonly reach a steady-state level after several years of implant duration in situ. Bordner et al. observed that serum ion levels peaked at 2-year follow-up, and then decreased to a steady-state level which was 50 % lower than peak levels [43]. Compared to preoperative levels, cobalt levels are approximately 15-fold higher while chromium is 5-fold higher, however, these elevated mean values (1 ppb for both ions) are still well below the cutoff value of 7 ppb [51]. These trends appear to be maintained when ion levels are measured at long-term (> 10-year) follow-up as well [52].

The prevalence of adverse reactions following MoM THA was evaluated by Stürup et al. in a study of 358 patients identified through the Danish Arthroplasty Register. The authors noted that at a mean follow-up of 3 ½ years, 50 patients (14 %) of reported groin pain, and that 15 of these (4 % of total cohort) had elevated serum ion levels [53]. Histologic evaluation of failed MoM arthroplasties showed that up to 85 % of cases had evidence ALVALs, 49 % had synovitis, 15 % had granulomas, and 14 % had evidence of isolated metallosis [51].

Implant survivorship is of paramount importance to both patients and surgeons. Recently published meta-analyses have demonstrated that stemmed MoM implants fail at a higher rate than MoP implants in comparable patient populations. Milošev et al. analyzed 10-year survivorship of metal-on-polyethylene, ceramic-on-ceramic, and metal-on-metal bearings in 469 patients. When revision for aseptic loosening as an endpoint was taken, stemmed metal bearings had significantly lower long-term survivorship (89 %) than polyethylene (99.5 %; $p = 0.001$) or ceramic (99 %; $p = 0.003$) [54]. In a recent meta-analysis comparing outcomes of MoM to conventional THA, Voleti and colleagues observed no differences in functional outcomes between

Table 3.6 Reported long-term revision rates from recent studies and national joint arthroplasty registry data

	Milošev et al.[a] [52] (%; 95 CI)	United Kingdom[b] [59] (%; 95 CI)	Australia[c] [13] (%; 95 CI)
Metal-on-polyethylene	1.6 (0–3.4)	3.6 (3.2–4.1)	8.9 (8.1–9.8)[d] 5.7 (4.8–6.9)[e]
Ceramic-on-ceramic	4.4 (1.7–7.2)	3.9 (3.6–4.5)	5.7 (5.2–6.3)
Metal-on-metal	12.1 (2.7–21.5)	12.5 (11.0–14.1)	14.1 (13.1–15.3)

[a] 10-year follow-up
[b] 8-year follow-up
[c] 11-year follow-up
[d] Reported as revision with conventional polyethylene
[e] Reported as revision with highly cross-linked polyethylene

the two bearings as measured by Harris Hip Scores, but observed significantly greater likelihood of complications (e.g. wound dehiscence, trochanteric bursitis) with metal bearings (OR 3.3; 95 % CI: 1.6–7.3) [17]. In general, implants which use smaller-diameter femoral heads (Table 3.2) have shown comparable long-term survivorship to MoP designs. Saito et al. reported long-term results of 90 hips in which a second-generation, small-diameter metal bearing was used [55]. At a mean follow-up of 12.3 years, the implant survivorship with revision for aseptic loosening was 98.8 %, while revision for any clinical reason was 94.4 %. Of the five revised hips in the study, one was revised for acetabular cup loosening, two were revised for recurrent dislocation, and two were liner exchanges following dissociation with the metal acetabular articulating surface from its polyethylene backing.

Although some specific implant designs have shown comparable survivorship to MoP bearings [54], these utilize small-diameter femoral heads and are prone to dislocate. The advent of larger femoral heads with thinner polyethylene shells brings into question the use of even these bearings which have not demonstrated clear superiority over currently available MoP designs.

Outcomes from National Joint Arthroplasty Registries

National joint arthroplasty registers are particularly useful for recording long-term implant surveillance data and reporting implant survivorship due to the large sample sizes which exceed what a single or multiple research centers may accomplish. Overall, there has been a substantial decrease in the use of MoM bearings. In the United Kingdom registry data have shown that all-metal hips have decreased from a peak annual use of 15,000 total hips in 2008 to less than 1,000 today [13].

Analysis of joint registry data has demonstrated that irrespective of country of origin, metal-on-metal THAs fail at a higher rate than metal-on-polyethylene or ceramic-on-ceramic bearings (Table 3.6) [56, 57]. Evidence of early failure of several MoM bearing designs were reported in the 2007 Annual Report published by the Australian Orthopaedic Association National Joint Replacement Registry (AOANJRR) [11], and subsequently confirmed by several follow-up studies [58, 59].

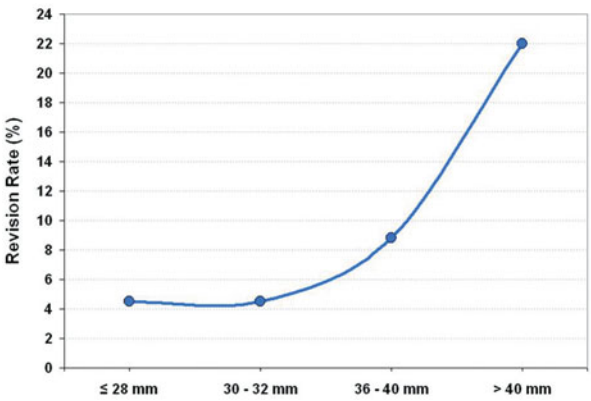

Fig. 3.1 Affect of femoral head size of the revision rates of MoM THAs at a final follow-up of 8 years. Data based on revision results from the Australian National Joint Registry

Data from the National Joint Registry for England and Wales at mid-term (mean 8-year) follow-up have demonstrated significantly higher revision rates of cementless metal-on-metal bearings (12.5 %) compared to cementless metal-on-polyethylene (3.6 %) or ceramic-on-ceramic (3.9 %) bearings at the same follow-up period [13]. These results have been mirrored by data from the Australian joint registry which reported a 14.1 % revision rate for metal bearings at 11 years compared to 8.9 % for metal-on-polyethylene and 5.7 % for ceramic-on-ceramic [13].

The affect of femoral head size has been well studied by the Australian National Joint Registry. At long-term follow-up (11 years), MoM bearings that use femoral head sizes less than 32 mm have similar revision rates compared to highly cross-linked bearings (5.8 % and 4.8 %, respectively), but better survivorship when compared to traditional high molecular weight polyethylene (9 %). However, when femoral head size is increased, a substantial increase in the revision rate at final follow-up is observed for 36–40 mm heads (12.5 % at 10-year follow-up) and > 40 mm heads (22 % at 8-year follow-up; Fig. 3.1).

The affect of modularity of the neck or the stem have also been evaluated by joint registry studies since the presence of a modular junction has been a point of concern [12, 60, 61]. Modular junctions may represent a source of wear between two non-articulating surfaces while at the same time the geometry and fit of the taper junction may create an electrochemical microenvironment which is highly susceptible to corrosion [60–63]. At a follow-up of 10 years the presence of a modular femoral neck was associated with higher revision rates in MoP hips compared to monoblock stems (11 % versus 6 %, respectively) but no difference was seen in the revision rates in MoM total hips at 6-year follow-up with modular or fixed femoral necks (10 % versus 10 %, respectively). However, the revision rate for MoM hips was still substantially higher at nearly half the follow-up period than MoP designs [12].

Conclusion

The role of stemmed MoM THA is greatly limited and potentially (or rapidly) becoming a contraindication for patients needing a THA from these multiple studies. The higher failure rates observed at mid- and long-term follow-up, as well as the risk of adverse local tissue reactions to metal debris, make metal bearings an unattractive clinical treatment option. While the use of a small-diameter femoral head (e.g. 28 mm) have demonstrated similar survivorship compared to MoP bearings, the need to use small head sizes may increase the risk for dislocations. With the recent development of large-diameter MoP bearings which have lower dislocation rates and highly cross-linked polyethylene liners which demonstrate improved wear characteristics, the potential uses for MoM bearings become limited. Although wear continues to be an issue, particularly for young patients who require a THA, metal bearings are likely in the future to continue to be superseded in clinical use by newer-generation ceramic and polyethylene designs.

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Chapter 4
Metal Reactivity: Its Influence on Primary and Revision Outcomes

George Grammatopoulos, Hemant Pandit, Adrian Low and David Murray

Introduction

Registry data has shown that although conventional metal-on-polyethylene total hip arthroplasty (MoPTHA) survival is excellent, an age effect can be demonstrated with higher revision rates seen amongst younger patients, especially men. The leading cause of revision in these patients is aseptic loosening, which has been shown to be associated with the amount of wear debris produced. This association stimulated interest in alternative bearing surfaces, such as metal-on-metal (MoM), which have potentially less wear production and could hence reduce the revision burden, especially amongst the younger patients [1–3].

Tribological lessons, from the survival and failure of first generation MoM prostheses, coupled with advancements in manufacturing engineering led to the re-introduction of MoM bearings in the 1990s [4, 5]. Successful reports of the Metasul (second generation) [6, 7], which was demonstrated to have high survival and low wear rates, stimulated further interest and led to the development of large diameter MoM bearings a few years later in the form of hip resurfacing arthroplasty (MoMHRA) and large diameter total hip arthroplasty (MoMTHA) (third generation) [8, 9]. Early, successful reports of third generation MoM implants led to their widespread use; it is thought that over one million have been implanted to date [10]. Such reports also influenced National Institute for health and Clinical Excellence (NICE), in recommending MoMHRA as an alternative to THA in young adults with end-stage hip arthritis, who are likely to live longer than the device is likely to last [11].

Over the recent years, it has become evident that wear-related complications occur with MoM articulations which can be a significant burden. These wear-related complications can occur either as a result of *metal reactivity/toxicity* (expected response

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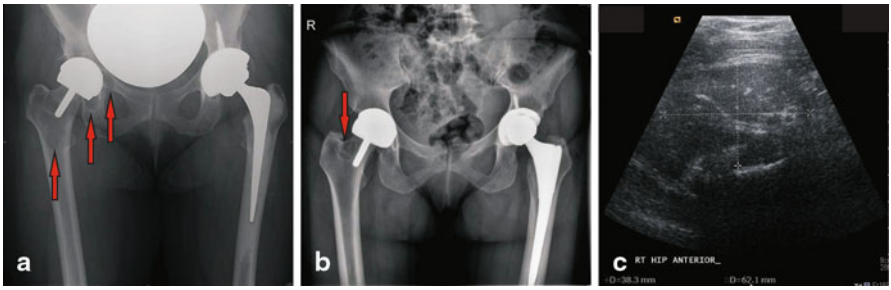

Fig. 4.1 Radiographic appearances of lytic areas around prosthesis (**a**, **b**). **c** Ultrasound scan findings around hip in radiograph *a*

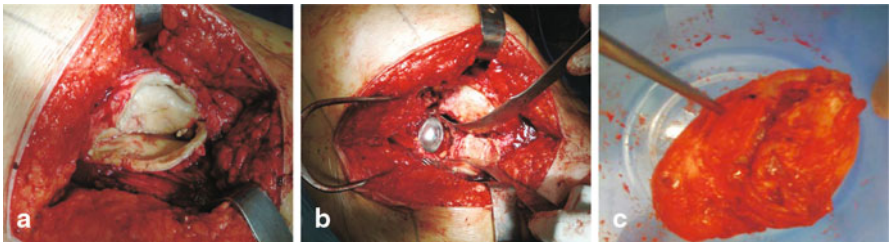

Fig. 4.2 Intra-operative appearance of a typical pseudotumour, demonstrating its encapsulated solid nature (**a**, **b**) and its appearance following *en masse* excision (**c**)

to an excessive/toxic wear load) or as a response of *metal sensitivity* (exacerbated response to an expected amount of wear load).

This chapter aims to define the burden associated with metal reactivity in MoM arthroplasty. In order to do so, we provide the reader with the current evidence on the effect of metal reactivity on a genetic/cellular and histological level and the influence of metal reactivity on primary and revision outcomes. In addition, we will also provide the reader with recommendations on what implementations need to be pursued in clinical practice in order to improve outcome. Lastly, we highlight topics of interest and questions that remain unanswered in this field.

Terminology

In 2008, Pandit et al. reported the first significant series of soft tissue masses associated with MoMHRA [12]. These soft tissue masses tended to be of either a solid, cystic or mixed nature. Clinically, patients presented with a variety of symptoms including pain, clicking, clunking, skin rash, palpable mass, dislocation or neurovascular compromise (Figs. 4.1 and 4.2). In addition, in the initial biopsy of these cases it was difficult to morphologically distinguish these masses from a

necrotic tumour. Based on these observations, these soft tissue masses were termed as "pseudotumour".

Other terms have also been used to describe these masses including aseptic lymphocytic vasculitis-associated lesions (ALVAL), cyst [13], mass [14], bursae [15], metal sensitivity [16], adverse reactions to metal debris (ARMD) [17] and adverse local tissue reaction (ALTR) [18].

Unfortunately, none of the names are ideal. Although the names have different definitions they all appear to cover different parts of the spectrum of reactions to metal. For example, metal sensitivity implies a hypersensitivity reaction but might exclude the toxic effect of metal debris. ALVAL is a histological diagnostic feature present in the majority of MoM revisions and not uniquely associated with these masses [19, 20]. A cyst or a bursa implies a fluid collection with a relatively thin capsule and excludes a mass. Conversely, an inflammatory mass might exclude a cyst. ARMD and ALTR are rather non-specific and do not convey the actual clinical nature of the problem. A pseudotumour is, by definition, an enlargement that resembles a tumour, resulting from inflammation, fluid accumulation, or other causes. It, therefore, not only covers the whole spectrum but also, like some of the other descriptions, includes lesions that could be unrelated to a MoM articulation. The term pseudotumour has been used previously to describe ill-defined masses in orthopaedic and other medical specialities' literature. It is, however, a controversial term as for the non-medical audience it has implications of cancer. Nevertheless, the word pseudotumour is an 'umbrella term' and is particularly useful as it describes the problem without implications about its cause; thus it will be used to describe these lesions in this chapter. In the context of MoM, pseudotumours are neither malignant nor infected. They cause a spectrum of damage ranging from a small indolent cyst or mass to local invasion with substantial soft tissue and sometimes bone destruction [12, 21]. Patients tend to present with pain, swelling, nerve damage, vascular claudication, spontaneous (pathological) fracture, late dislocation or with a clunking hip. A small proportion may present with systemic conditions such as cardiomyopathy, thyroid dysfunction, as well as visual and neurological disturbances. Some authors have referred to the latter as 'arthroprosthetic cobaltism' [22].

Patho-Aetiology

Pseudotumours are thought to occur secondary to a reaction to wear debris. Kwon et al. showed that pseudotumours were associated with elevated levels of metals ions in patients' serum and hip aspirates, which are surrogate markers of wear [23]. There was up to a six-fold elevation of serum metal ion levels and 13-fold elevation of hip aspirate metal ion levels in patients with pseudotumours compared to patients without pseudotumours. Similarly, Langton et al. showed that hips with pseudotumours had elevated serum chromium and cobalt ion levels in comparison to asymptomatic controls [17].

In vitro analysis of explants has demonstrated high wear rates of both the femoral and acetabular components. When compared to controls, both the femoral and acetabular components of pseudotumour cases demonstrated higher linear wear. Glyn-Jones et al., measured the wear of failed MoMHRAs and reported significantly higher (linear and volumetric) wear in the pseudotumour cases compared to the controls [24]. In addition, there was a significantly higher prevalence of edge wear in pseudotumour cases compared to controls. The authors also noted that 2 out of the 18 pseudotumour implants were associated with low wear (< 4 μm/year), which raises the possibility that excessive wear is not the sole driving force to pseudotumour development and that the individual response to any amount of wear might vary substantially. Similarly, the observation that 4 out of the 18 controls had high wear (> 4 μm/year) and did not develop a pseudotumour re-enforces the above hypothesis of the significance of the individual's response. These findings have led to the hypothesis that pseudotumours can occur either as a result of metal reactivity/toxicity (expected response to an excessive/toxic wear load) or as a response of metal sensitivity (exacerbated response to an expected amount of wear load).

We recently conducted a histological analysis of MoMHRAs revised for pseudotumour and correlated the histology findings with the extent of wear [25]. The histology was carried out by a musculoskeletal pathologist (Dr Nick Athanasou); histological features evaluated semi-quantitatively included the extent of necrosis and the nature of the inflammatory cell infiltrate, including ALVAL. The ALVAL response is thought to be indicative of the immune inflammatory response and possibly delayed hypersensitivity [26, 27]. Bearing surface wear was measured using a non-contact, optical coordinate measuring system (Redlux) in a blinded fashion. Wear measurements obtained included linear wear (μm) and volumetric wear (mm^3) of each femoral and acetabular component. This allowed for estimation of total (femoral + acetabular) linear and volumetric wear. Knowing survival of each MoMHRA, we were able to calculate the total linear wear rate (TLWR) as: Total linear wear rate (μm/year) = Total linear wear (μm)/Implant survival (years).

In our recent study, substantial necrosis and a heavy macrophage infiltrate were noted in most periprosthetic tissues, including all pseudotumours, many of which contained a significant ALVAL infiltrate. Most pseudotumours were associated with highly worn prostheses (80 %). It was noted that the extent of necrosis and macrophage infiltration correlated with the volume of generated metal wear. Although increased wear volume moderately correlated with a high ALVAL response, all pseudotumours with low wear had a strong ALVAL response. We can hence conclude that the majority of pseudotumours (80 %) are associated with increased wear and that the increased in vivo wear is associated with necrosis and a heavy non-specific foreign body macrophage response coupled with a variable adaptive or specific immune response (ALVAL). A minority of pseudotumours (20 %) are associated with low wear and all had a significant immune response.

Hence, even if surgeons were to minimize wear of MoM prostheses with appropriate patient/implant selection and surgical practice; some pseudotumours would still occur (20 %) due to the variability in the immune response between patients.

Tribology

Wear Mechanism

Wear in MoM bearings is characterised by an initial high wear rate, known as the run-in phase, followed by a lower wear rate termed as steady-state wear. As the bearing surface is subjected to contact stresses, the micro-structure of the surface changes and can incorporate organic material from the lubricant fluid in the joint forming the tribolayer; which generally has a finer grain structure than the bulk material forming the rest of the implant [28].

Wear-simulator studies have shown MoM bearings to have up to 100 times less wear than MoP bearings [29]. Similarly, hip joint simulator and retrieval studies have shown that MoM wear rates are sensitive to material properties (carbon content, material process, heat treatment), design (clearance, subtended angle of the acetabular component) and manufacturing process (surface roughness, tolerance, sphericity) [30, 31].

Simulation studies have shown that under optimal conditions, low volumetric wear rates exist, typically in the order of $< 1\,mm^3$ per million cycles [29], and wear debris particles produced are predominantly in the nanometre size range (40–80 nm) [32]. In order for low wear to occur, the femoral and acetabular components should be orientated in such a way that the contact patch (area of contact between the two components) does not occur at the edge of the acetabular component. Such component positioning allows for an entrainment wedge to form, which in turn aids lubricant to enter between the bearing surfaces [33].

Lubrication is essential for optimal function of the MoM bearings; MoM implants exhibit increased wear when the fluid film lubrication is disturbed, leading to inability to form or maintain the tribolayer. This typically occurs under edge loading conditions (contact patch on the head comes into contact with the edge of the rim). Edge loading could theoretically occur as a result of either rotational or translational mal-positioning [28, 34]. Simulator studies have shown that rotational mal-positioning (primary edge loading) can lead to wear of 1–5 mm^3/million cycles, whilst translational mal-positioning (secondary edge loading) has been shown to further increase wear rate as much as 10–100 mm^3/million cycles [35–37].

In addition to the earlier section, further mechanisms of failure have been described in total hip arthroplasties (THAs). The presence of a tapered femoral neck connecting the femoral head to the femoral stem, adds an additional metal coupling interface which has recently been reported to be a possible alternative source of wear [38, 39]. Frictional torque at the bearing surface is thought to be translated from the femoral head to the neck, with subsequent damage at the taper. In addition, there has been one report of failure due to fretting corrosion of cemented stems [40].

Wear Particles and Ions

Cobalt (Co) and chromium (Cr) are the principal elements of the CoCr alloy used in all MoM. Both Co and Cr are naturally occurring trace elements vital for biological function [41]. Although the wear rates of MoM implants are lower than the conventional MoP articulation, the number of nanometre sized particles produced is greater than the number of micrometer sized particles produced in MoP articulations [32, 42]. For a MoM hip implant, it has been estimated that an average of 6×10^{12}–2.5×10^{14} particles are being produced per year, which would equate to 500 times more particles than a MoP articulation (5×10^{11} particles/year) [32]. The size of the particles is thought to vary between 30 and 500 nm [32, 42]. The majority are oval in shape, although some appear to be needle-shaped. Most of the smaller particles have been shown to be chromium oxide, whilst the larger ones are cobalt-chrome-molybdenum (CoCrMo) particles.

The MoM wear debris may exist in a number of states, including metallic particles produced by mechanical wear and the products of corrosion. Exposure to extra-cellular fluid leads to the formation of a passive layer of corrosion upon all exposed surfaces of metal including the articulating surface and wear debris [43]. X-ray photoelectron spectroscopy (XPS) analysis of this corrosion layer reveals high levels of carbon, oxygen, nitrogen and chromium compounds, with trace amounts of metallic and oxidized cobalt. These constituents may dissolve in both intra- and extra-cellular fluids leading to the presence of ionic species namely Co^{2+}, Cr^{3+} and possibly Cr^{6+} [44, 45]. The metal ions released from the metal particles are thought to produce the systemic effects, as they have been shown to circulate freely in the body, whereas the metal particles probably cause the local effects [46, 47]. Depending on the chemistry of the biological environment, various corrosion products can be produced including metal–protein complexes, inorganic metal oxides and salts.

Metal Reactivity and Cytotoxicity

The cytotoxic effect of nano-particles is poorly understood, with much of the present knowledge coming from in vitro reports [46–48]. Of particular relevance to pseudotumours are the studies on macrophages and lymphocytes, as both of these cell lines are characteristic histological features of pseudotumours. Kwon et al. reported a significant dose-dependant decline in macrophage viability with cobalt nanoparticles (30–60 nm) and Co^{2+} ions; however chromium nanoparticles and Cr^{3+} failed to produce a significant reduction in cell viability at the same concentrations [47]. As a possible mechanism, the particles may be taken up by the cells and within the acidic environment of the phago-lysosome, the particles corrode and release ions into the cells. The high concentration of Co ions within the cell then kills the cell [47]. The cell contents and particles are then released and cause further damage by a vicious cycle of cell death and release of particles. The increased cytotoxicity capability of cobalt ions over chromium ions was also reported in an earlier study by Catelas et al.

[46]. The authors were able to demonstrate a significant reduction in macrophage viability occurring at 8–10 ppm for Co^{2+} and 350–500 ppm for Cr^{3+} ions. The effects of Cr^{6+} and Co^{2+} on human lymphocyte number and function were studied by Akbar et al. [48]. A significant reduction in cellular viability and increase in apoptosis was seen with high concentrations (10–100 μM) of both ions. Cell proliferation and function (i.e. cytokine release) were affected with non-toxic concentrations. Similar to the aforementioned studies, lymphocytes in the Akbar et al. study appeared to be more susceptible to Co^{2+} than Cr^{6+}.

The size of the wear particles produced may also be an additional factor determining the type of response. Yue et al. examined the effect of particle size on macrophage cellular response, and reported that nanoparticles accumulate at a faster rate than micron-sized particles in macrophages [49]. Nanoparticles were found to transport within the macrophage via the lysosomal pathway, whilst larger particles accumulated in the cytoplasm.

Metal Reactivity and the Genetic Effects

A variety of transition metals are known to be mutagenic and genotoxic at relatively low concentrations, a result of metal induced oxidative stress, chromosomal aberration or disruption to DNA repair and maintenance mechanisms. Currently, the International Agency for Research on Cancer (IARC) has classified implanted metallic cobalt as class 2B—"possibly carcinogenic to humans", and implanted metallic chromium as "not classifiable" [50, 51]. However, compounds containing hexavalent chromium are described as class 1—"carcinogenic to humans".

There have been several in vitro studies demonstrating the mutagenic and genotoxic effects of Co and Cr [52–56]. Cobalt is considered less genotoxic than chromium; both exerting their genotoxic effects via various intra-cellular mechanisms. In vivo studies on peripheral lymphocytes of MoM patients showed increased lethal and non-lethal aneuploidy and chromosomal translocations that correlated with metal ion levels [57]. The detectable genetic damage was reduced following revision to a MoP device.

However, despite the above in vitro observations, there has been no in vivo direct link between MoM wear and subsequent risk of carcinogenesis. Visouri et al. showed no increase in the incidence of any type of cancer and reported mortality rates of patients who had a MoM device implanted equal to, or lower than those of the general population [58, 59]. Similarly, data-linkage studies between Joint Registry and various national health outcome databases have thus far not shown an increased risk of cancers in patients with MoM hip implants [60]. However, it is important to note the potentially long latency period between exposure to a carcinogen and development of cancer. Hence, further studies are warranted in order to study the long-term effects, if any, of exposure to wear (MoM) particles and subsequent carcinogenesis.

Outcome After MoMHRA

Much interest has recently been focused on investigating the outcome following MoM arthroplasties, including the effect of metal reactivity. Common study end points have been patient-reported outcome measures (PROMs) and incidence/prevalence of failures due to pseudotumours.

Patient Reported Outcome and Metal Reactivity

Kwon et al. studied the prevalence of pseudotumours about *asymptomatic* MoMHRAs. As per study protocol, the authors reviewed patient-reported outcome measures, metal ion levels and radiological assessments of all hips including ultrasound scans [61]. The Oxford Hip Score (OHS), a validated assessment tool, was used to establish patient's perception of their hip pain and function [62, 63]. The OHS has 12 questions and has a score range of 0–48 with a higher score equating to a better outcome [63]. The study included 201 MoMHRAs, the majority of which were unilaterally resurfaced patients ($n = 115$). At a mean follow-up of 61 months (minimum of 3 years), the authors identified an overall pseudotumour prevalence per patient and per MoMHRA of 4.4 and 6.5 %, respectively. Patients with detectable pseudotumours had significantly higher serum metal ions levels of both cobalt (9.2 vs. 1.9 ppb) and chromium (12 vs. 2.1 ppb) in comparison to non-pseudotumours ($p < 0.001$). The authors also noted that although the study patients were recruited under the assumption of being asymptomatic, the patients with previously undetected pseudotumours had significantly inferior OHS (41 vs. 47) in comparison to non-pseudotumours ($p < 0.001$). From the Kwon et al. study, it is evident that the patients with highly wearing prostheses have lower functional outcome which may be secondary to the wear process itself (e.g. impingement related pain with secondary increased wear) or an aftermath of the local effects of the wear products (cobalt synovitis, pseudotumour around hip).

Williams et al. investigated the prevalence of pseudotumour in *asymptomatic* patients, with high (> 80) Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), at a minimum of 2-years post-surgery [64]. Their study's cohort included MoMTHAs ($n = 31$), MoMHRAs ($n = 25$) and MoPTHAs ($n = 24$). Radiological assessments were made by an ultrasound performed by two sonographers. The authors reported alarmingly high pseudotumour prevalence rates amongst both MoM implants (32 % in MoMTHA and 25 % about MoMHRA). Interestingly, one of the MoPTHAs had evidence of a cystic mass around the hip. As found in the Kwon et al. study, higher ion levels were detected amongst the pseudotumours, however significance was not detected which was attributed to the study's small numbers. In Williams et al. study, the authors failed to mention whether hips with associated pseudotumour had inferior WOMAC scores compared to the non-pseudotumour cases, similar to the findings of Kwon et al.

Malek et al. reported on the findings of all *symptomatic* patients reviewed, following MHRA [65]. Their study reported on 209 patients with unilateral MoM implants (19 MoMHRAs and 190 MoMTHAs), with metal ion levels and Magnetic Resonance Imaging (MRI) results. The authors reported pseudotumours, as per MRI findings in 84 patients (40 %), six amongst the MoMHRAs (32 %) and 78 amongst the MoMTHAs (41 %) [65]. Hart et al., in a case-control study reported an equally high prevalence of pseudotumour in 30 patients with a painful MoM prosthesis and 28 patients with an asymptomatic MoM prosthesis [66]. Using metal-artefact reduction sequence (MARS) MRI, the prevalence of pseudotumour was 57 and 61 %, respectively.

Lastly, Van Der Straeten et al. reported on a large cohort of unilateral ($n = 453$) and bilateral ($n = 139$) MoMHRA patients in a single, independent, surgeon series [67]. The authors included strict criteria in order to group patients into well and poorly functioning, including no patient-reported symptoms, no surgeon-detected abnormal clinical findings, well-functioning hips (Harris Hip Score > 95), well-orientated acetabular components and lack of abnormal radiographic findings. Patients in the well-functioning group had significantly lower serum metal ion levels (threefold) in comparison to those in the poorly-functioning group ($p < 0.001$), for both unilateral and bilateral MoMHRAs.

Survival of Primary MoM Arthroplasties and Pseudotumour

MoMHRA

The published short-term (≤ 5 years) MoMHRA survivorship rates have varied between 75 and 100 % (Table 4.1). Data from national registry reports and studies have shown an implant-specific risk factor for survival [68, 69]. The ASR system MOMHRA (DePuy, UK) has shown poor early/mid-term survivorship in both independent center studies, as well as in the national registry data, and this subsequently led to the withdrawal of the ASR resurfacing system. For other hip resurfacing systems, the mid-term data (5-year survival) were encouraging with survival of 88–99 %, which was similar amongst designer and non-designer series. Treacy et al. reported a 5 year survival of 98 % [3]. Independent studies by Steffen et al. [2] and Hing et al. [70] reported 5 year survival rates of 95 and 98 %, respectively. In all these early-term survival studies (≤ 5 years), femoral neck fracture was the most common failure mode and revision due to pseudotumour only accounted for 0–0.5 % of cases.

Pseudotumour revisions have mostly been described following the first 2 years post-MoMHRA surgery [12, 17, 71]. A review of the literature demonstrates variability in the incidence of revision across different centres, which can be attributed to many factors including patient selection, implant selection, implant placement and surgical factors. However, these studies are only early/mid-term with a mean follow-up of 3 to 4 years [72]. Hence, longer follow-up studies are needed, given that it has been hypothesised that the cumulative revision rate will increase with time. Most

Table 4.1 Survivorship of the various hip resurfacing implants

Study	Implant	Number of hips	Gender (% males)	Age at surgery (years, range)	Follow-up (years, range)	Survivorship for revision (%)
Bergeron et al. [90]	ASR	228	80	54 (25–73)	3 (2–5)	95
Langton et al. [39]	ASR	418	56	56 (28–77)	4 (2–6)	75
Daniel et al. [1]	BHR	446	79	48 (26–55)	3 (1–8)	99
De Smet et al. [91]	BHR	252	n/a	49 (16–75)	3 (2–5)	98
Hing et al. [70]	BHR	230	66	52 (19–82)	5 (4–6)	98
Steffen et al. [2]	BHR	610	59	52 (16–81)	4 (2–8)	95
Ollivere et al. [92]	BHR	463	66	56 (20–70)	4 (1–9)	96
Treacy et al. [73]	BHR	144	74	52 (17–76)	11 (10–12)	94
Coulter et al. [75]	BHR	230	66	52 (18–82)	10 (10–12)	95
Holland et al. [35]	BHR	100	74	51 (21–68)	11 (10–13)	92
Murray et al. [93]	BHR	646	59	52 (16–81)	8 (0–12)	87
Amstutz et al. [94]	C+	350	77	41 (14–49)	5 (2–9)	94
Amstutz et al. [95]	C+	1,000	75	50 (14–78)	6 (1–11)	95
Amstutz et al. [74]	C+	100	66	49 (15–71)	12 (11–13)	89
Spencer [96]	Cormet	747	n/a	n/a	3 (2–6)	95
Naal et al. [97]	Durom	100	70	53 (20–72)	5 (4–6)	88

ASR articular surface replacement, *BHR* Birmingham hip resurfacing, *n/a* information not available from paper

of the data on mid/long-term (≥ 10 years) MoMHRA survivorship is from designer or high volume surgeon series. These 10-year survival rates vary between 89 and 97 %. Treacy et al. reported a survival rate of 94 % at 11 years [73], whilst Amstutz et al. reported on a 12-year survival of 89 % [74]. Recent reports from independent, experienced, high volume surgeons from both the UK and Australia have reported 10 year survivals of 94.5 and 95 %, respectively [75, 76]. Furthermore, the incidence of revision due to pseudotumour in these reports varies between 0 and 2.0 %. In order to define the mid-/long-term outcome of MoMHRA and define the incidence of revisions due to pseudotumours, our group performed a survival study of all BHRs (Smith & Nephew, UK) performed at the Nuffield Orthopaedic Centre which is an independent, tertiary referral, multi-surgeon teaching hospital in the UK and aimed to define the 10-year survival and patient outcome. In addition, this study aimed to detect the incidence of revision due to pseudotumour with the BHR implant, on a cohort previously reported to have a 5-year survival of 95 %. The 10-year survival of the whole cohort was 87.1 % and the overall incidence of revisions due to pseudotumour was 7.5 % (Fig. 4.3). As previously reported, the survival and patient-reported functional outcome depended on gender and implant size [75, 77]. In women ($n = 267$) the 10-year survival was 74 %, the 10-year revision rate for pseudotumour was 18 %, the Oxford Hip Score (OHS) was 43 (SD: 8) and the UCLA activity score was 6.4 (SD: 2) (Fig. 4.4). In men ($n = 379$), the 10-year survival was 95 %, the 10-year revision rate for pseudotumour was 2 %, the OHS was 45 (SD: 6) and the UCLA score was 7.6 (SD: 2). In the most demanding subgroup, men younger than 50 years old treated for primary osteoarthritis, the survival was 99 %. In contrast, young men

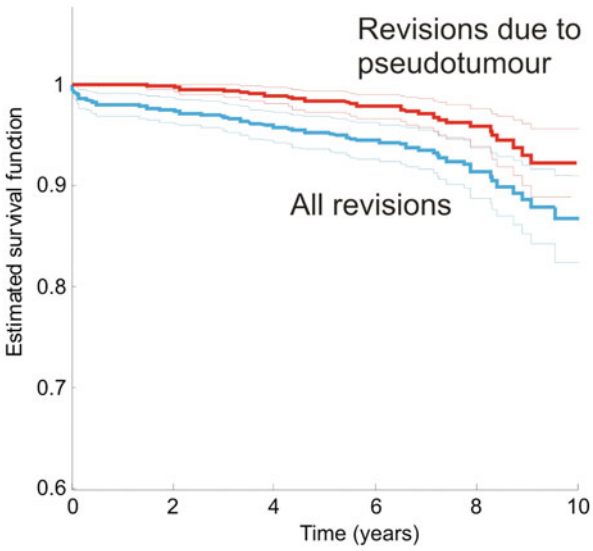

Fig. 4.3 Kaplan Meier survival curve for the BHRs at the Nuffield Orthopaedic Centre. Graph is colour coded as per revision indication

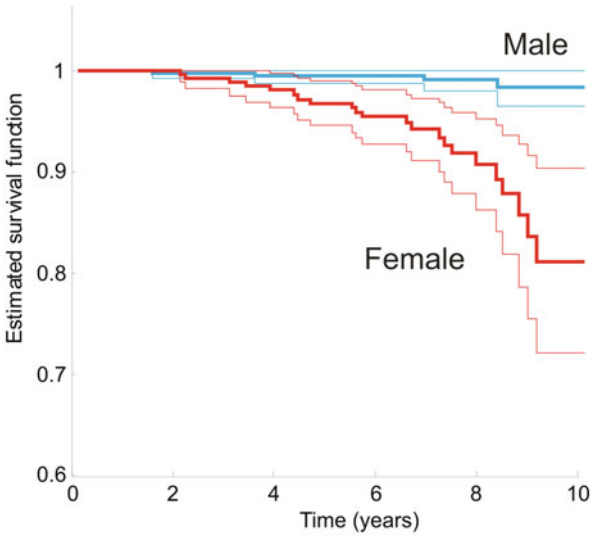

Fig. 4.4 Incidence of revision due to pseudotumour at the Nuffield Orthopaedic Centre with the BHR. Graph is colour coded as per gender

tend to have problems with conventional THA, as shown by the Swedish Hip Joint Registry, with survival of 85 % at 10 years [11]. As most of the registry data relate to a conventional polyethylene and metal articulation, it would be interesting to compare our study's findings with the results of modern bearing couples such as ceramic-on-ceramic and metal-on-highly cross-linked polyethylene. Early and mid-term results for those bearing couples show good survival and outcome [78, 79] but longer, 10-year data are needed in order to make valid comparisons for the optimal treatment option of a young man with end-stage hip disease.

As these same patients were studied a few years earlier, these findings have allowed us to evaluate the evolution in the failure modes. Steffen et al. reported on the 5-year survival of the first 610 BHRs performed in this study's cohort and reported overall survival was 95 %. Twenty-three revisions were reported and fracture was the most common indication for revision ($n = 12$) followed by aseptic loosening ($n = 4$); pseudotumour was only reported in three revisions. In the current 10-year study of 54 revisions, there was no increase in the number of fractures reported and aseptic loosening only accounted for two more revision cases. However, there was a great increase in cases that were revised due to pseudotumour with 23 extra cases (total $n = 26$) and a small number of cases revised due to pain with clinical evidence of impingement ($n = 8$). From our ongoing studies of these patients, pseudotumour is the most commonly encountered mid-term (5–10 years) MoMHRA failure mode.

The prevalence of pseudotumours amongst all MoMHRAs revised at two specialized tertiary referral, European centres (the Nuffield Orthopaedic Centre (NOC), Oxford, United Kingdom and the ANCA Clinic, Ghent, Belgium) was reviewed by Grammatopoulos et al. [80]. Between June 1999 and December 2010, 236 MoMHRAs revisions in 224 patients were performed. The majority of patients were females ($n = 137$, MoMHRAs = 146). The most common indication for revision was the presence of a pseudotumour, accounting for 112 MoMHRAs (48 %), followed by fracture ($n = 34$, 14 %) and painful impingement ($n = 32$, 14 %). It was noted that the annual revision burden had risen in both units over a 12-year period. During the first 6 years (1999–2004), 28 revisions were performed in both centres. However, over the following 6 years, the revision burden appears to have risen by seven-fold, with 208 revisions performed within this later period.

MoMTHA

Donnell et al. were the first to report a high failure rate amongst MoM hip arthroplasties [40]. The authors reported a failure rate of 14 % at 5 years with the Ultima hybrid (Depuy International Ltd), 28 mm MoMTHA with a cemented, polished, tapered femoral component. It was shown that the corrosion taking place between the cement and the polished stem was the most likely cause.

Langton et al. reported on the failure rates amongst the ASR implants [39]. The authors reported on the mid-term survival for both MoMHRA ($n = 418$) and MoMTHA (with Corail or S-ROM stems) ($n = 87$). The failure rates due to pseudotumour were 25 % for the MoMHRAs and 49 % for the MoMTHAs at 6 years.

Bolland et al. reviewed the outcome of 199 hybrid MoMTHAs in a single surgeon series [38]. The implants used were the collarless polished tapered (CPT) stem and the BHR acetabular components. Femoral heads used were those of Midlands Medical Technology (MMT) until they were replaced by the ADEPT resurfacing head following purchase of MMT by Finsbury Orthopaedics. The authors reported a failure rate of 10 % at 5 years; failure was related to female sex and larger head sizes. Smith et al. analyzed 402,051 primary total hip replacements (of which 31,171 were stemmed MoM) in the National Joint Registry of England and Wales, performed

between 2003 and 2011 [81]. The overall 5-year revision rate of MoMTHA (ASR implants excluded) in young females was 6.1 %, which was much higher than other bearing couples (3.3 % CoC and 1.6 % MoP).

Outcome After Revision

Outcome After Revision

Ball et al. were the first to report outcome following MoMHRA revision [82]. The authors reviewed the outcome of 21 MoMHRAs converted to MoMTHAs due to femoral component failures (fracture and loosening). In 18 hips the acetabular component was retained and in three hips both components were revised. The converted patients were case-controlled, matched for age, gender and indication for surgery with 64 patients that had undergone primary MoMTHA during the same period by the same surgeon. There was no significant difference between the two groups with regard to operative time, blood loss or complication rates. Furthermore, no significant differences were observed with regards to Harris Hip Score (HHS), UCLA activity and SF-12 scores. The authors concluded that conversion of a MoMHRA to a primary MoMTHA, due to a femoral side failure, appeared to be comparable to a primary MoMTHA in terms of surgical effort and clinical outcome.

Our group performed a retrospective case-controlled study in order to define the outcome following revision due to all modes of failures, including pseudotumour [21]. This study included the first, consecutive, 53 failed MoMHRAs requiring revision, and conversion, to THA (the cases) at our center. The controls were matched for gender, age at primary surgery, pre-operative diagnosis and length of follow-up. In order to determine how serious of a complication pseudotumour is, we assessed the outcome of MoMHRA revision for pseudotumour and compared this to the outcome of other MoMHRA revisions, as well as the outcome of matched primary MoP THAs.

At an average follow-up of 3.0 years (1–7 years) the outcome of MoMHRA revision for pseudotumour ($n = 16$) was poor (OHS: 21) and was significantly ($p < 0.0001$) worse than the outcome of MoMHRA revision for fracture ($n = 21$) (OHS: 40) or for other causes ($n = 16$) (OHS: 38). The clinical outcome of MoMHRA revisions for pseudotumour was also significantly ($p < 0.001$) worse than the outcome of matched primary THA, but was similar ($p > 0.05$) to these patients before they had their THA. In contrast the outcome of MoMHRA revisions for fracture and other causes was not significantly different from the outcome of matched primary THA (Fig. 4.5). The most prominent intra-operative finding of pseudotumour cases was that of soft-tissue destruction and necrosis, with associated bone loss. Pseudotumours tended to pass through tissue planes. As evident by the intra-operative records, revision surgery was often difficult, particularly in cases with massive soft-tissue destruction or neurovascular involvement. The neurovascular involvement failed to fully resolve after surgery and hence patients had persistent neurological and claudication type of symptoms (three femoral nerve palsies, one femoral artery stenosis).

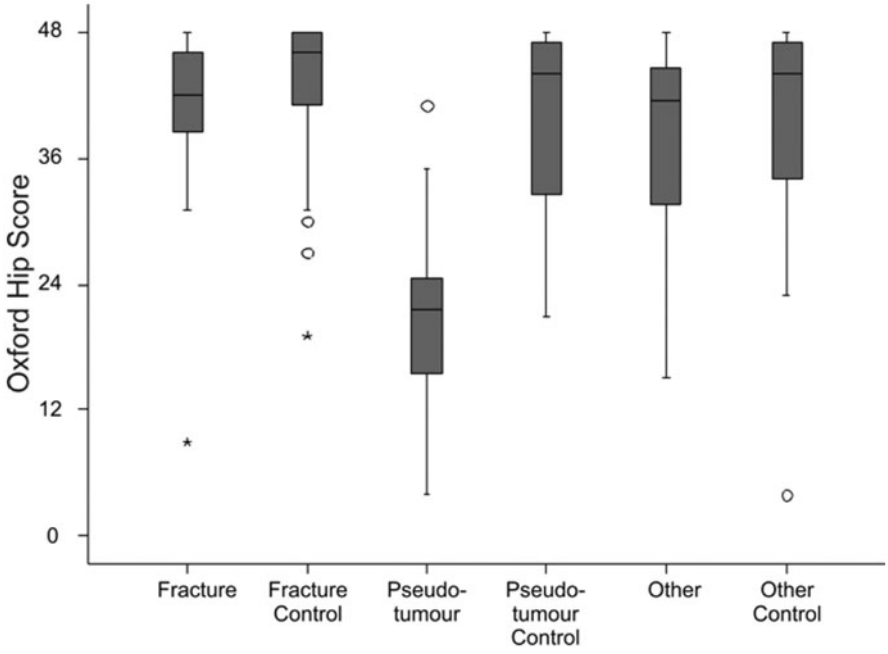

Fig. 4.5 Differences in OHS between the three MoMHRA revision groups and their controls

Following pseudotumour revisions there were three recurrent dislocations (Fig. 4.6), and two cases of component loosening. Six cases required re-revision at which evidence of recurrence of pseudotumour was identified. The incidence of major complications following revision for pseudotumour (50 %) was significantly ($p < 0.02$) higher than following revision for other causes (14 %).

The findings of this study suggest that outcome after revision of MoMHRA is dependent upon the revision indication. In revisions for reasons other than pseudotumour, the outcome was generally good and similar to that after primary THA. However, it is evident from our study that pseudotumour is potentially a catastrophic complication following MoMHRA. This study reflects our initial experience of pseudotumour revisions in our center. The condition was unknown amongst referring hospitals and clinicians at the time. As a result, a significant number of patients presented late having seen a number of surgeons at other hospitals; in fact a number of patients in our studies presented to the tumour surgeons with a large palpable mass and a working diagnosis of sarcoma. This delay in recognition and treatment likely compromised outcome due to the extensive loss detected at revision.

The effect of increased awareness and experience in dealing with pseudotumour at revision was reported by De Smet et al. [83]. In a retrospective, consecutive, single-surgeon, case series the authors reviewed the outcome of revision of 113 failed MoMHRA and reported that mid-term outcome (Harris Hip Score, complication and re-revision rates) following MoMHRA revision can be improved. Factors that were

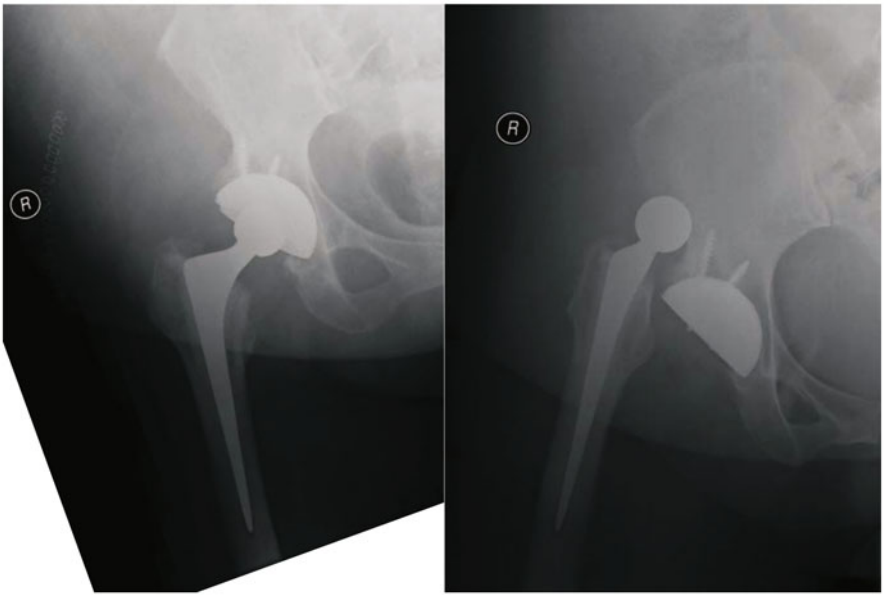

Fig. 4.6 Radiographs of a pseudotumour case, revised to a hybrid (THA) with a 32 mm femoral head that dislocated within weeks post-op

identified to improve outcome included: increased awareness of the failure modes, the use of diagnostic aids such as metal ions, the use of femoral heads of greater diameter at revision and patient education. The improved outcome reported with increasing experience was also observed in cases with pseudotumours. De Smet et al, noted that, with increased awareness, the pseudotumours revised were associated with less soft-tissue destruction, which probably contributed to improved outcome.

In a small proportion of cases, the pseudotumour can recur possibly as a manifestation of incomplete clearance during the initial revision. The reason for the pseudotumour reoccurrence is not completely known. A possible cause may be an ongoing reaction to remaining metal debris. In cases with intra-pelvic extension or pseudotumour in close proximity with neurovascular structures, complete excision of the pseudotumour is indeed difficult if not impossible at times.

Current Management Guidelines for MoM hip Implants

Although a significant proportion of patients with MoM hips have undergone revision surgery, a much larger proportion of patients remain relatively asymptomatic with well-functioning hips. The latest data from the England and Wales National Joint Registry (NJR) and the Australian NJR have reported survivorships of 88 % at 7 years and 87 % at 10 years respectively [68, 69]. At present it is unclear as to how

Table 4.2 Table illustrating different management recommendations for asymptomatic patients with MoMHRA and MoMTHA as per various protocols

	FDA	MHRA		EFORT
	All MoM	MoMHRA	MoMTHA	All MoM
Follow-up	Every 1–2 years	According to local protocol	Annually if diameter ≥ 36 mm	Annually first 5 years (then according to local protocols)
Soft tissue imaging	No	No	No (unless metal ions rise then US or MARS MRI)	No (unless XR abnormal or Co >2 to 7 μg/L then US, CT or MARS MRI)
Metal ions	No	No	Yes (blood)	Yes (blood or serum)
Consider revision		Abnormal imaging and/or rising metal ions		Abnormal imaging and/or rising metal ions; Co >20 μg/L

many of these will develop a pseudotumour in the future. Some studies, as discussed in this chapter, have reported a high prevalence of pseudotumours even amongst asymptomatic patients with MoM implants [61, 64].

Large cohorts of patients are being actively monitored to varying degrees according to local/national guidelines or protocols [84–89]. This has significant cost implications both for the health services as well as for the patients. Usually, the monitoring involves frequent follow-up (at least yearly in most cases) and may include periodic blood metal ion measurements and/or soft tissue imaging. We believe that current guidelines could be enhanced and may not be sufficiently sensitive to detect many of these subclinical pseudotumours. The decision of whether and how to monitor these patients and when (if) to offer revision surgery needs to be better defined by the local/national organizations.

Management guidelines for all patients with a MoM hip are currently issued by national regulatory agencies and professional organizations such as the FDA (Food and Drug Administration) in the USA, MHRA (Medicines and Healthcare products Regulatory Agency) in the UK and EFORT (European Federation of National Associations of Orthopaedics and Traumatology) in Europe [84, 85, 87–89]. Their recommendations attempt to integrate local experiences with current best evidence and aim to serve as a useful resource for all health care professionals. However, these recommendations differ significantly as outlined below in Table 4.2.

EFORT recommends annual follow-up for the first 5 years with plain radiographs (XR) and metal ion measurements for all asymptomatic patients with a MoM hip [88]. If there is an abnormality on clinical examination or XR or if cobalt (Co)-values are above a certain threshold (2–7 μg/L; exact level still to be determined) then cross-sectional imaging (Ultrasound, US; Computed tomography, CT; and/or Metal Artefact Reduction Sequence, MARS MRI) should be performed. Revision

is considered when pathological findings are present on any cross-sectional imaging study and/or a further significant increase of Co-level has occurred. Small fluid collections on cross-sectional imaging indicative of pseudotumour needs close monitoring. Revision is considered for Co > 20 μg/L even in asymptomatic cases with normal imaging studies because of fear of osteolysis, tissue necrosis and long-term ill-health secondary to hypercobaltism.

The MHRA recommends annual follow-up and metal ion levels for asymptomatic patients with MoMTHAs [89]. Cross-sectional imaging (MARS MRI or US) is performed if blood metal ion levels rise, and revision surgery should be considered if imaging is abnormal and/or blood metal ion levels are rising. A fluid collection alone, unless it is very large, can be safely monitored without the need for revision surgery. The MHRA recommends that asymptomatic MoMHRAs be followed-up "according to local protocols" without any need for metal ion levels or cross-sectional imaging. FDA recommends regular clinical evaluation for asymptomatic patients with MoM hip implants, typically at least once every 1–2 years [85]. Soft tissue imaging and metal ion testing is considered unnecessary if the surgeon feels the hip is functioning properly.

There are several differences between FDA, EFORT and MHRA guidelines that may cause confusion. FDA and EFORT do not differentiate between the monitoring of patients with MoMTHA and MoMHRA while MHRA does. MHRA specifies use of blood metal ion levels (either cobalt or chromium), EFORT accepts either blood or serum levels (of only cobalt) while the FDA emphasizes consistency by using the same sample type, same measurement method and preferably the same laboratory. FDA and EFORT consider computerized tomography (CT) an acceptable imaging modality, whilst MHRA does not. EFORT recommendations are based upon absolute metal ion levels while the MHRA places more significance on change in the (rising) metal ion levels rather than absolute levels, but does recognize that blood metal ion levels > 7 μg/L indicates potential for adverse soft tissue reaction. FDA does not believe there is a clear need to routinely check metal ion levels in an asymptomatic patient or to utilise a specific metal ion level as a trigger for revision surgery. MHRA and EFORT have stated that revision should be considered if both metal ion levels and imaging studies are abnormal but can be considered in the presence of normal imaging studies if Co > 20 μg/L (EFORT) or if the metal ion levels are rising (MHRA). It is evident that EFORT guidelines reflect a greater concern in Europe over MoMHRA implants than in the UK where they are essentially managed like any other hip replacement (MHRA). Use of imprecise terms such as a "small" fluid collection, "abnormal" or "pathological" imaging findings and "significant" increase in Co-value, has the potential to limit the practical application of both EFORT and MHRA guidelines. Furthermore, none of the guidelines have clear recommendations for incidental finding of large pseudotumours.

Current FDA, MHRA and EFORT guidelines are not sensitive for subclinical pseudotumours. There are sufficient studies suggesting a high prevalence of asymptomatic pseudotumours, (up to 60 % as one study suggests [64]), and also that the metal ion levels in blood or serum are not a sensitive screening tool, especially for MoMTHAs [65]. Cross-sectional imaging is the most sensitive technique to detect a

pseudotumour. Therefore, with the current guidelines, all pseudotumours associated with a MoM implant in the USA or the UK will not be detected as long as the patient remains asymptomatic because neither metal ion levels nor imaging are indicated (FDA and MHRA). A pseudotumour associated with a MoMHRA implant in Europe will only be detected in an asymptomatic patient if Co levels are > 2–7 μg/L which is the level at which imaging studies are indicated (EFORT). Therefore, all pseudotumours that occur in the presence of normal metal ion levels will be missed. In asymptomatic patients with MoMTHA, subclinical pseudotumours will be detected in the UK only if metal ion levels rise (MHRA), in Europe if Co levels are > 2–7 ug/l (EFORT) and in the USA if the orthopaedic surgeon feels that the hip is not functioning properly.

Conclusions, Suggestions for Improving Outcome and Future Studies

The unanticipated emergence of pseudotumours, secondary to metal wear debris, has ensured that the rapid uptake of MoM hip replacements during the last decade would be surpassed by an even more abrupt decline in its use. Pseudotumour is the most common cause for MoM implant revision where the risk of formation is influenced not only by patient and implant factors but also by factors which are under the control of the surgeon such as cup placement. Therefore, proper patient/implant selection and optimal implant placement by the surgeon may improve the outcome of primary MoM hip replacements.

Pseudotumours tend to occur only after a few years of implantation and the incidence is believed to increase with time but it is unclear whether this increasing trend will continue beyond the mid-term to significantly impact on long-term implant survival. Based on current evidence, it is not advisable to continue using large diameter head MoMTHA, as alternative bearing couples have significantly better survival rates. However, MoMHRA may still be considered an option for young active males where low pseudotumour rates and high long-term implant survival have been reported.

The initial experience of revision MoM hip surgery for pseudotumour was associated with poor patient outcomes and high rate of re-operations [21]. It was hypothesized that the lack of general awareness and understanding of the condition at the time may have led to delayed diagnosis and resultant increased soft tissue and bony destruction. The majority of re-operations were for dislocation and pseudotumour recurrence. Therefore, adequate pseudotumour clearance and use of large diameter femoral heads that reduce the risk of re-operation as well as increased awareness leading to prompt diagnosis and potentially less soft tissue damage are factors which may improve outcomes following revision surgery (Fig. 4.7). It would be of benefit to test this hypothesis by comparing the outcome after revision of the initially revised pseudotumour cohort with a later cohort of patients that experience earlier intervention.

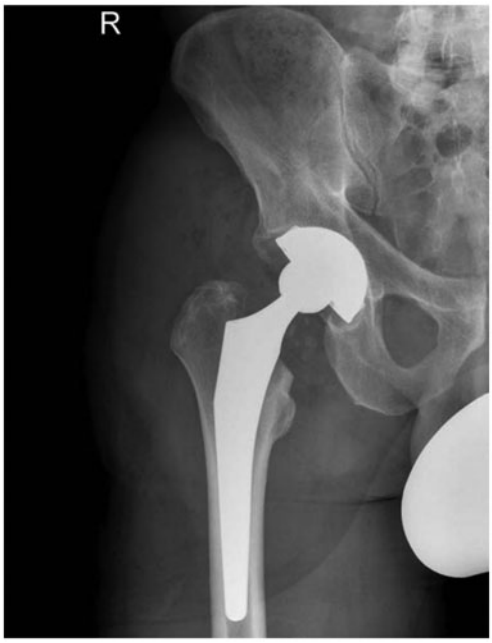

Fig. 4.7 The use of a dual mobility cup in revision for pseudotumour

As the most symptomatic MoM hips have been revised, there remain an even greater number that have not been revised, remain asymptomatic and are under surveillance. In addition, some patients are keen to have their MoM hip revised despite any significant abnormality detected. With an increasing number of studies reporting high prevalence of asymptomatic pseudotumours, this large population of asymptomatic MoM hips could pose future logistical and clinical dilemmas. Who to screen, which investigation and how frequently, when to revise? These are just some of the unanswered questions. The majority of asymptomatic pseudotumours will remain undiagnosed if current partially defined guidelines are followed. Prospective studies documenting the natural history of asymptomatic pseudotumours in MoM hip patients are required.

Finally, MoM hip implants have not yet been associated with an increased risk of malignancies in current studies. Some cancers can have long latency periods, and continued long-term studies and outcomes should be pursued.

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Chapter 5
Are Metal Ion Levels a Trigger for Surgical Intervention?

David Langton

The Clinical Implications of Elevated Blood Metal Ion Concentrations

It is unquestionable that metal-on-metal (MoM) hip arthroplasties cause significant increases in serum and blood concentrations of chromium (Cr) and cobalt (Co) [1].

Beyond this, there is little agreement about what risks, if any, these elevations present to the host. Potential long-term adverse systemic health effects should not be ignored. This chapter, however, will focus on the factors associated with metal ion release from contemporary large-diameter MoM hip arthroplasties and the local complications which may result.

Adverse Reactions to Metal Debris

Adverse reaction to metal debris (ARMD) is a term used to describe a range of local pathologies seen in association with MoM hips that include soft tissue necrosis, large sterile joint effusions, metal staining of tissues, pseudotumours and osteolysis [2, 3]. Although the extent of soft tissue lesions does not appear to be dose-related to metal debris exposure [3, 4], there is accumulating evidence to show that such reactions are far more likely to develop if an MoM prosthesis is wearing at a greater rate than expected [3, 5]. There is no convincing evidence in the existing literature documenting a severe tissue reaction to a well-functioning (in tribological terms) unilateral MoM prosthesis. That is not to say that this cannot happen—but the evidence suggests that it is uncommon. Other potential source contributions of metal debris such as neck taper junctions also should be considered when evaluating hip arthroplasties and their impact of the surrounding tissues.

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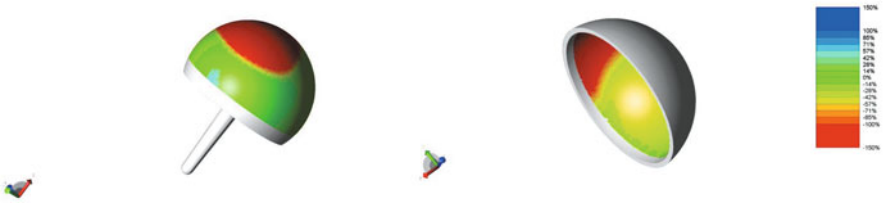

Fig. 5.1 Typical wear map of a failed hip resurfacing. *Red areas* indicate wear of greater than 10 μm. Volumetric wear rate was greater than 30 mm^3/year in this case. Typically as is seen in cases of excessive bearing surface wear, blood Co concentration was 92 μg/L and Cr was 40 μg/L. Joint fluid levels showed the usual paradoxical concentration ratio associated with excessive bearing wear with Cr concentration of 11,000 μg/ and Co 4,500 μg/L. Gross metallosis and osteolysis was encountered at revision surgery though soft tissue necrosis was not extensive. Note that even with such elevated wear rates a large proportion of the bearing surface remains within the as-manufactured form (*green areas*)

Identifying Atypical Wear: Characterizing and Quantifying Wear

Please note that for the purposes of this chapter, "wear" is defined as material removal from metallic surfaces. In reality, the mechanisms leading to metal release are complex and involve interaction between friction and corrosion (tribocorrosion). It is legitimate to use the term "wear" as a catch-all term in this context as the elimination of friction between two components (the head and the cup for the bearing, the stem and head at the taper junction) would eliminate the vast majority of debris production.

Volumetric and linear wear analysis of retrieved MoM components has been performed since the 1990s [6]. According to the current literature, coordinate measuring machines (CMM) and Redlux are the most commonly used modalities to carry out these measurements [7, 8]. While a contacting probe is used in the former versus light waves in the latter, the fundamental principles are the same: the unworn surface is identified; a complete idealised surface is then generated based on this unworn surface and then compared to the areas where material has been lost. This can be done relatively easily due to two factors. Firstly, particularly in the most worn samples, maximum material loss occurs in discreet, localised areas of the head, cup and tapers. This phenomenon has been described by a number of authors after examination of explants and those taken from hip simulator studies [9, 10]. Large portions of the bearing and taper surfaces are thus left relatively undisturbed (Figs. 5.1 and 5.2). This begs the question: How is the unworn area identified? Advancements in manufacturing technology led to the reintroduction of MoM because components could now be produced which were much smoother and rounder than before. One of the critical principles underpinning the hope for the successful function of contemporary MoM arthroplasty was that these precision-manufactured components could harness a beneficial fluid film [11]. This enhanced lubrication would lead to a reduction in wear rates [12]. Manufacturing data confirms that heads, cups and tapers

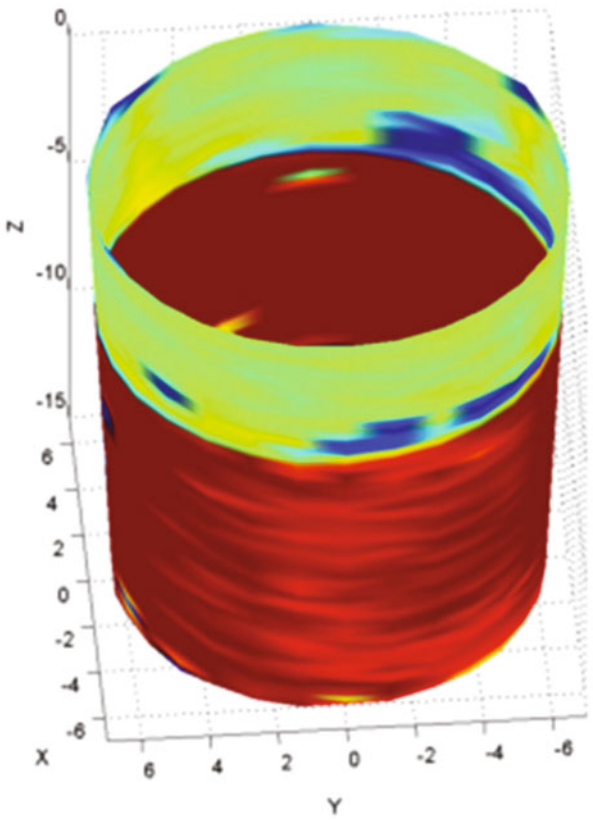

Fig. 5.2 Wear map of the internal surface of a femoral head retrieved from a female patient with 36 mm Pinnacle total hip replacement (THR). Bearing surface wear rate was 1.2 mm^3/year but the taper wear rate was more than 1.5 mm^3/year. Joint fluid showed the typcial Co–Cr ratio associated with taper failure with Co of 2400 μg/L and Cr of only 300 μg/L. The taper showed the typical pattern of material loss—maximal damage occurred where the trunnion base had engaged leaving the surface untouched distal to this area

are manufactured with extremely tight tolerances. To all intents and purposes, they are near-perfect spheres and cones. When a retrieved femoral head is scanned, for example, it can be scanned in sequential segments and the measured points used to calculate the "form" of the sphere (or in more simplistic terms—how round the sphere is). If the measured form matches the manufacturing tolerance, it is, therefore, reasonable to assume that this area has not worn significantly in vivo. As an example, in the case of explanted MoM heads and cups which have worn at similar rates to polyethylene, it is normal for over 50 % of the bearing surfaces to remain indistinguishable to the as-manufactured form. The remainder of the bearing surface in cases such as these can be as much as 1 mm larger than they should be (the cups which wear from inside to out, making the measured radii larger) or 1 mm smaller for the heads (which wear from outside inwards, making measured radii smaller than the original surface) [13].

Blood, Serum and Hip Joint Fluid Metal Ion Analysis

All metal ion values reported in this chapter were obtained using Inductively Coupled Plasma Mass Spectroscopy (ICPMS) which is currently accepted to be the preferred mode of blood metal ion measurement [14, 15]. The analyses were carried out solely

at United Kingdom trace element laboratories which participate in the Trace Element Quality Assurance Scheme (TEQAS). This scheme is a collaboration between seven centres in the United Kingdom which perform trace element analysis using the same techniques and regularly monitor results between units to ensure reproducibility [16]. Blood samples were placed into ethylenediaminetetraacetic acid (EDTA) tubes and serum samples into plain tubes. The quantification limits for both Cr and Co were less than 0.2 μg/L and the within assay reproducibility was 2 % at a concentration of 8 μg/L.

Background Blood Levels of Cr and Co

There are no large-scale data on background metal ion concentrations. In 2007, a study was commenced to address this deficiency by analysing the background environmental exposure to various heavy metals in the North of England [17]. Blood samples were taken from a random sample of informed volunteers from the National Blood Service (NBS) which is part of the National Health Service Blood and Transplant (NHSBT) service. The study population consisted of subjects aged 17–70 years who had passed the screening health protocols for the NBS. Pregnant women and those with children up to 9 months old were excluded, as were transient populations. It was not known whether individuals had metallic implants at the time of venesection. When a blood donation was taken, the first 8–12 mL were diverted into a sample pouch and then into two BD Vacutainer® Plus blood collection tubes (Beckton Dickson, New Jersey, United States) containing K2EDTA (ethylenediaminetetraacetic acid).

A total of 3042 patients gave samples. The mean (range) age of the patients was 45 (16–72) years. There were 1527 male and 1515 female patients. The median (range) Cr concentration was 1.5 μg/L (below detection limit—8.6) and for Co was 0.5 μg/L (0.3–6.7). Shapiro Wilk test for normality showed that neither Cr nor Co was normally distributed ($p = 0.001$, $p = 0.002$ respectively). Ninety-eight (3.2 %) patients were found to have blood Cr concentrations > 2 μg/L whereas only one patient (0.03 %) was found to have a blood Co concentration > 2 μg/L. Of the 3042 patients, 2831 (93.1 %) had a Co less than 1 μg/L. When patients were subdivided by sex and age range, median concentrations of Cr and Co in the various subgroups varied by no more than 0.1 μg/L.

Hip Resurfacing and Total Hip Replacements: Different Systems, Different Failure Rates, Different Mechanisms of Failure, Different Metal Ion Concentrations

It should be clearly stated at the outset that MoM hip resurfacing and MoM total hip replacements (THRs) are different implant systems with distinctive surgical demands. Journal articles and conference organisers rarely emphasise this design

difference. Understandably, large-diameter metal bearing surfaces, so heavily marketed in the last decade, have seized the attention of surgeons and researchers alike. Yet National Joint Registries have shown a clear difference in the performance of the two different systems [18]. Only in the last couple of years has this narrow focus broadened to appreciate the importance of other areas of metal debris release—most notably the taper junction. Modular junctions of orthopaedic implants were intensively studied in the 1990s [19, 20]. It was clear at that time that junctions were another source of anxiety, a potential Achilles' heel. It is now becoming increasingly apparent that this anxiety was justified [14].

This chapter is divided, therefore, for the reasons detailed above, into two parts: hip resurfacing and THR.

Metal Ion Concentrations in Patients with Hip Resurfacings

How Do Metal Ion Concentrations Relate to Wear of MoM Prostheses?

In 2008, De Smet et al. described the highly significant relationship between serum metal ion concentrations and the linear wear of retrieved femoral resurfacing components [21]. Building on this knowledge, we examined the relationship between the volumetric wear of 91 retrieved unilateral hip resurfacings and the corresponding pre-revision blood and serum Cr and Co values. In this study, eighty-two hips had been revised secondary to ARMD, two were revised for loose titanium-backed cups, one hip was revised due to infection, two for avascular necrosis (AVN), two for pain with an unknown cause, one for painful impingement and one for uncomplicated femoral fracture.

Linear regression using logged values of bearing surface wear rates as the independent variable and logged blood/serum concentrations as the dependent variables returned adjusted R^2 values of 0.855 for blood Co ($p < 0.001$), 0.756 for blood Cr ($p < 0.001$), 0.813 for serum Co ($p < 0.001$) and 0.785 for serum Cr ($p < 0.001$). An R squared value of 1.000 would tell us that 100 % of the variation in the metal ion concentrations is explained by the volumetric wear rates. Here the R squared value for blood Co was 0.855, showing that the relationship between blood Co and measured wear is extremely strong. Other factors which may potentially explain the remaining variation are patient activity at the time of the blood test [22], measurement error of the volumetric wear [23], irregular wear rates and/or patient-specific variation.

The equation of the best fit line was used to normalise the logged values in order to translate the results into real clinical values. The results are illustrated in Fig. 5.3 and tabulated in Table 5.1 which compares whole blood Co concentrations and wear rate.

Metal Ion Concentrations as Screening Tests for Atypical Bearing Surface Wear

While the relationship between metal ion concentrations and the amount of material loss from retrieved components is powerful, it is logical and thus not unexpected. Of

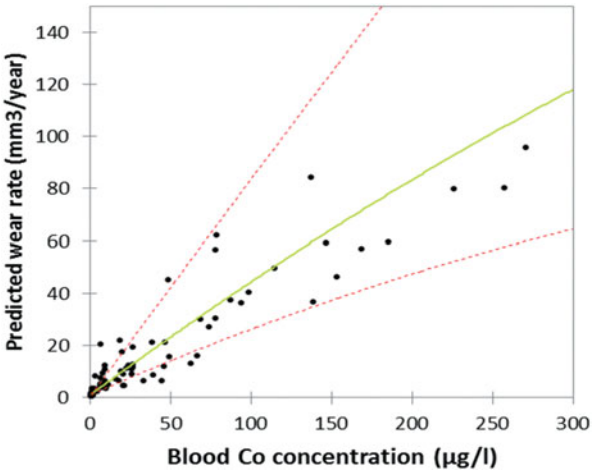

Fig. 5.3 Blood Co concentrations and their relationship to the predicted wear rate of the retrieved bearings. The *red dashed lines* indicate 95 % confidence intervals

Table 5.1 Whole blood concentrations and MoM implant resurfacing wear

Whole blood Co (µg/L)	95 % CI rate of wear (mm^3/year)
0.5	0.47–0.64
1	0.77–1.16
2	1.26–2.10
3	1.68–2.96
4	2.07–3.79
5	2.43–4.58
10	4.00–8.28
15	5.35–11.7
20	6.58–14.9
30	8.80–21.1
40	10.8–27.01
50	12.7–32.7
100	20.9–59.0
150	28.0–83.4
200	34.4–107
250	40.3–129
300	46.0–151

greater relevance to practising clinicians is the reliability of ion tests to differentiate between implants which are performing optimally or suboptimally in vivo. We attempted to address this issue by constructing receiver-operating characteristic (ROC) curves to assess the sensitivity and specificity of different blood fractions and different elements to detect abnormal wear. For such methodology "abnormal wear" had to be defined at certain threshold levels. These threshold levels were assigned following consideration of a number of factors, including our own experience and previously published data. Sieber's study of retrieved second generation MoM hip components provides a guide to the expected performance of "improved" third- and fourth-generation designs. Using a CMM, Sieber et al. found that the average

volumetric wear rate was 0.3 mm^3/year [24]. This value is close to those reported in simulator studies. Our experience of analysis of failed MoM revised for loosening or taper failure suggests that these figures are not overly optimistic, and it is generally accepted that well-functioning bearing surfaces should wear less than 1 mm^3/year. Although relatively small, there are inaccuracies and reproducibility errors in wear analysis [13, 25] and wear rates can be exaggerated by shorter durations in vivo, particularly when the bedding in phase may skew calculations [26]. For this reason, we performed ROC analysis using generous values of 2 and 3 mm^3/year. To put these values into clinical context, in the largest analysis of its kind, the lowest wear rate of a hip resurfacing associated with ARMD was approximately 2 mm^3/year [3].

It must be noted that there are inherent weaknesses in retrieval studies of this kind. It is not possible to remove devices from patients with low blood metal ion levels who are satisfied with their joints. Without autopsy banks, these retrieval studies will always suffer from these limitations. Despite this, the results were remarkably consistent. A number of failures could reliably be put down to causes other than those specific to the metal bearing surfaces. The wear rates in these cases were indeed low, and the corresponding blood tests were, without exception, also low.

Blood Co concentrations above 2 μg/L were suggestive of increased wear rates although specificity was unacceptably low, especially when 2 mm^3/year was designated "abnormal". ROC analysis showed whole blood Co to have the most clinically appropriate sensitivity and specificity for the detection of abnormal wear. A whole blood Co concentration of greater than or equal to 4.5 μg/L appeared to be the most reliable clinical threshold value after the consideration of the sensitivity and specificity as well as the confidence limits. Whole blood Co greater than or equal to 4.5 μg/L had a 90.4 % (95 % CI, 81.1–95.5 %) sensitivity and 94.4 % (72.0–100.0 %) specificity for detecting abnormal wear of greater than or equal to 2.0 mm^3/year (Fig. 5.4). When "abnormal wear" was defined as greater than or equal to 3 mm^3/year, clinically the most useful threshold level appeared to be a blood Co concentration of 5.04 μg/L. This value showed a sensitivity of 92.8 % (83.7–97.2 %) and specificity of 95.5 % (76.2–100.0 %).

Elevated Metal Ion Concentrations in Asymptomatic Patients with Hip Resurfacings

The Food and Drug Administration (FDA) guidance on the on the management of asymptomatic patients with MoM hips [27] stated that "If the orthopaedic surgeon feels the hip is functioning properly and the patient is asymptomatic, the FDA does not believe there is a clear need to routinely check metal ion levels in the blood." The justification of this statement was that "elevated blood metal ion levels in the absence of symptoms have been reported in a limited number of research studies for some MoM hip implant patients. These studies are difficult to interpret because: . . . the correlation between elevated blood metal ion levels and development of future local or systemic adverse reactions is not well established."

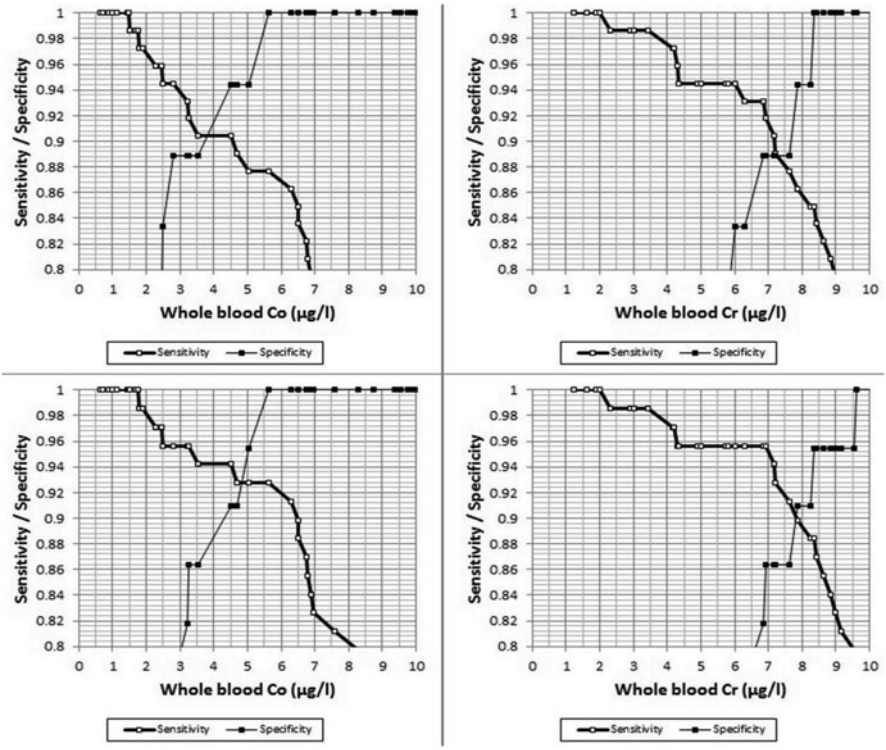

Fig. 5.4 Sensitivity and specificity of blood Co and blood Cr to identify wear defined at 2 mm^3/year (*top right* and *top left*). The equivalent plots (*bottom left* and *right*) have been constructed using abnormal wear at 3 mm^3/year

Recent guidance put forward by the Medicines and Healthcare Regulatory Agency (MHRA) of the United Kingdom also did not recommend that patients with MoM hip-resurfacing arthroplasties should undergo routine blood metal ion testing in the absence of symptoms "unless the patient cohort is of concern". It went on to state that a Cr or Co level greater than 7 µg/L "indicates the potential for soft tissue reaction" [28]. But this guidance was primarily based on a cross-sectional study which compared patients with failed MoM hips to control patients with "well-functioning" MoM hips [29]. In this study, a hip was defined as "well-functioning" if the patient was asymptomatic, irrespective of the blood metal ion concentrations. In fact, several patients assigned to the "well-functioning" hip group had blood Co concentrations in excess of 5 µg/L and one was in excess of 50 µg/L. These patients then acted as the control group to determine whether blood metal ion testing was legitimate to identify problems in clinical practice. The post-operative time at which samples were taken was not controlled for, nor was an attempt made to compensate for time as a confounding factor.

It is likely that patients exposed to increased metal debris may show temporary "tolerance" to the stimulus and a certain time period must elapse or a threshold

exposure be reached before an immune response is established and symptoms develop. Several publications include descriptions of patients who were initially pain free but went on to develop pain a number of years later [2, 3, 29]. Furthermore, increased metal ion levels in asymptomatic patients may be associated with underlying pathology, including osteolysis [3, 30, 31]. It is well recognised that osteolysis can be silent, often only manifesting in the form of radiographic changes or pain secondary to loosening of components [31, 32]. Cross-sectional studies, therefore, may present us with a distorted representation of a developing clinical picture.

As has been shown, blood metal ion testing provides the surgeon with the power to assess the tribological performance of the prosthetic joint in vivo [13, 21]. It is not unreasonable, therefore, to suggest that the performance of the joint in a tribological sense should be included when control groups are assigned.

With these principles in mind, we conducted a statistical study based on a cohort of asymptomatic patients who had given blood for metal ion analysis. In 2007, unusual tissue reactions were observed in a small number of patients implanted with the Articular Surface Replacement (ASR) device at University Hospital of North Tees. As a matter of clinical need, patients with ASR (manufactured by Depuy, Leeds, United Kingdom) and Birmingham Hip Resurfacings (BHRs, manufactured by Smith and Nephew, Warwick, United Kingdom) were brought back to clinic for review, and blood metal ion testing was offered to all patients. During these review appointments Harris Hip and University of California, Los Angeles (UCLA) activity scores were documented. Subsequently, patients were followed up at a maximum of 12 months between appointments and blood tests repeated, if possible. Until it became clear that excessive wear/metal ion concentrations were significantly associated with the development of ARMD [33], clinical decisions were not based on these results.

All patients who had given blood between 2007 and 2010, who had no or "slight" pain, no radiological abnormalities and a Harris Hip Score [34] greater than or equal to 95 at the time of venesection were identified and their clinical courses documented. There were a total of 278 patients with 299 resurfacing hip prostheses. Of these, there were 246 ASR and 53 BHR prostheses. The mean (range) post-operative follow up of the patients was 70 months (12–118). The mean (range) follow up post venesection was 36 months (2–63). Two patients had died in the study period of unrelated causes. All patients underwent clinical reviews at a minimum of 2 years post venesection unless they had undergone revision surgery. At the time of writing, 41 joints had been revised (36 ASRs and 5 BHRs). All but one of these prostheses (an ASR revised secondary to avascular necrosis in a male patient) were revised secondary to ARMD. Twenty-five of the ARMD prostheses were revised in female patients and 15 in male patients.

A statistical model was then created to examine the relationship between a patient's initial recorded blood Co concentration and the risk of the development of joint failure secondary to an ARMD. For the purposes of the prosthetic survival analysis, the end points were: the last documented clinical review; the patient undergoing revision surgery prior to March 2012 for any reason other than ARMD; or patient death. Subjects were censored if they had undergone revision surgery for ARMD. We then used a Cox-proportional hazards model to investigate risk factors for failure secondary to ARMD following the hip-resurfacing procedure.

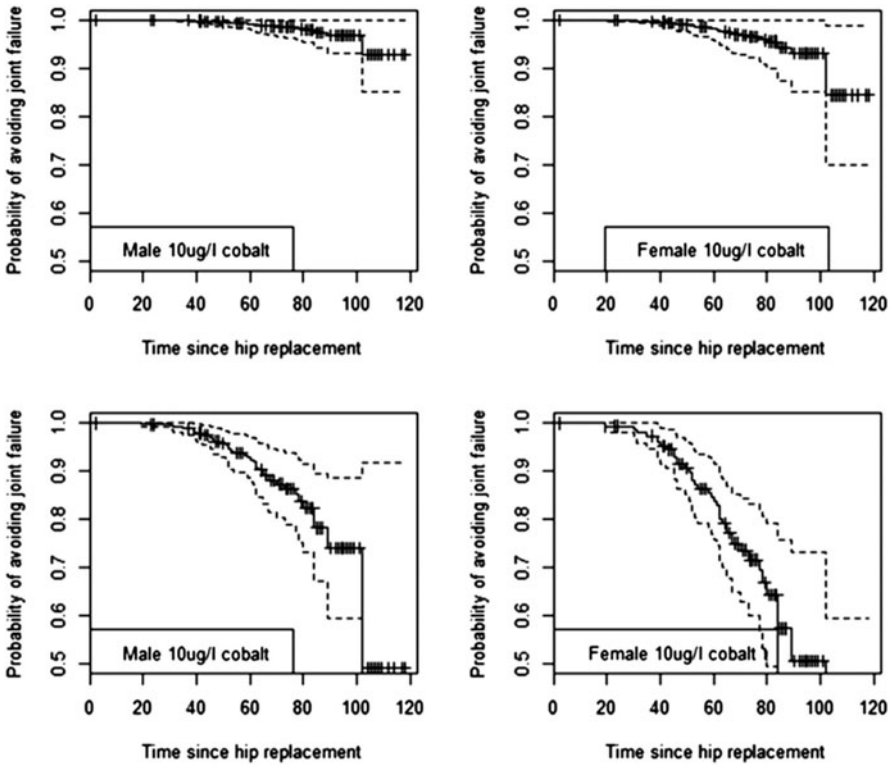

Fig. 5.5 Predicted survival curves for hip replacements for two male and two female hypothetical individuals with blood Co concentrations of 10 μg/L. Device is the Birmingham Hip Resurfacing (*top two plots*) and Articular Surface Replacement (*bottom two plots*). Time period is in months. Survival curves shown with 95 % CI

Analysis of hip resurfacing-failure using Cox-proportional hazards models indicated that males had a 66 % lower risk of joint failure than females ($p = 0.0218$). The level of blood Co was a positive and significant risk factor ($z = 8.44$, $p = 2 \times 10^{-16}$) as was the device, where the BHR posed a significantly reduced risk for revision by 89 % ($p = 0.00005$). A best-fitting model was then employed to predict the likely individual survival curves of MoM devices for males and females at three levels of blood Co (2, 5 and 10 μg/L). The survival curve for ASR and BHR patients with blood Co concentrations of 10mg/L are shown in Fig. 5.5. They illustrate the increased risk of ARMD if patients are female, fitted with an ASR device and have elevated blood Co concentrations. As an example, a female with an ASR and 10 μg/L of Co in her blood has a 38.8 % chance of avoiding a replacement by 7 years post replacement, whilst a male has a risk of 67 %. Equivalent probabilities for BHR females and males with the same Co levels at 7 years are 94.2 and 97.4 %, respectively. ASR and BHR male and female patients with blood Co concentrations of 2μg/L were found to have more than 98 % chance of avoiding ARMD at 7 years.

The results of the study suggested that elevated blood Co levels are a matter of concern, even in asymptomatic patients. These findings run contrary to the current MHRA and FDA guidance. Female patients appear to be at greater risk of joint failure than male patients with equivalent Co concentrations, particularly at lower levels. This might indicate an increased propensity of female patients to mount an adverse immune response. The pathological spectrum of ARMD has been described in detail in our previous work [35]. One of the histological hallmarks of this response is Aseptic Lymphocyte Dominated Vasculitis Associated Lesion (ALVAL) [36]. In this condition, lymphocytes form thick cuffs around blood vessels. In its most advanced stage, lymphoid neogenesis is observed, and blood vessels can become hyalinised and obliterated [35]. Tissue specimens from joint capsules affected by rheumatoid arthritis share some histological similarities with ALVAL tissue retrieved from patients with failed MoM joints and it is accepted that the incidence of a number of immune conditions such as rheumatoid disease is higher in women [37]. It does not seem unreasonable, therefore, to suggest that women are predisposed to the development of ALVAL especially when one considers that, invariably, reports of local pathologies associated with MoM prostheses include a disproportionate number of female patients [2, 33, 38]. We had previously, perhaps erroneously, attributed this observation entirely to the fact that smaller-diameter resurfacings (used more in females) generally wear at a greater rate than equivalent larger joints [39]. We speculate there is a gender-specific difference which may be linked to sex hormones.

There also appeared to be a difference in the failure rates of the ASR and BHR joints at equivalent blood Co concentrations. An explanation for this unexpected finding could be that wear debris released from the ASR bearing surface can more readily stimulate an immune cascade. It is well documented that wear volume and particle morphology can determine the resulting periprosthetic immune response [40–42] and it was for this very reason that MoM joints were introduced. It was thought that the overall reduction in volumetric wear rate and the smaller size of particles liberated from MoM prostheses would avoid the initiation of macrophage (histiocyte)-driven osteolysis caused by polyethylene debris [43]. Leslie et al. [44]. presented evidence that there is a significant difference in the morphology of ASR and BHR particles, with the median size of ASR particles being approximately half the size of BHR particles. If this is true, it would mean that ASR joints wearing at the same volumetric rate as a BHR joint expose the patient to a far greater number of particles.

While at lower concentrations ASR patients seemed to be at greater risk of the development of ALVAL, when patients were exposed to very high levels of Co ($> 10\ \mu g/L$), the risk of development of osteolysis greatly increased in both the ASR and BHR patients. The periprosthetic tissues of patients with Co concentrations in this category were often riddled with macroscopically visible metal wear particles [35]. Histological analysis, without exception, showed heavy infiltration of macrophages (histiocytes) [35]. This macrophage-dominated response (similar to the response to polyethylene wear particles) is consistent with hip simulator data which have shown that particles released under harsh wear testing are much larger than those released under ideal wear conditions [45]. Again, the suggestion is that the morphology of

the wear debris may be critical. Unfortunately, in this series of patients, only in those with advanced bony defects which required grafting were there any obvious changes on plain radiographs. We are now performing computed tomography (CT) in patients with extremely elevated blood metal ion concentrations in order to better assess bony integrity and aid pre-revision planning.

The overall findings showed that blood metal ion concentrations are a useful clinical tool even in asymptomatic patients. Ion concentrations, if low, can be reassuring to both patients and surgeons and can also allow rationalisation of resources. Grossly elevated ion concentrations indicate the risk of early prosthetic failure and can be used to direct further investigations or implement closer follow-up. Patients with extremely high levels should be considered at high risk for the development of osteolysis. At our unit, which acts as a referral centre for the treatment of failed MoM joints, in total 40 patients with blood Co concentrations greater than 20 μg/L have undergone revision of their hip resurfacings so far. All were found to have macroscopic metal staining of the local tissues and 35 were found to have some degree of bone loss. In light of these findings, at our unit patients with grossly elevated metal ion concentrations are now offered revision surgery in the absence of symptoms.

Total Hip Replacements

Failure Rates

The 2011 report of the National Joint Registry for England and Wales (NJR) [46] published failure rates of 29.0 % for the ASR total hip replacement (THR) at 6 years, in contrast to a 9.6 % failure rate for the ASR resurfacing implant. This indicates a dramatic difference in the performance of the two systems despite identical bearing surfaces. Some observers have stated that the failure of the ASR THR can be linked directly to the flawed design of the ASR acetabular component, leading to higher friction that propagates distally, stressing the modular junction and leading to release of debris from the taper junction [47]. However, joint registry reports from England and Wales have shown that MoM THRs in general have not performed as well as conventional bearing surfaces. As shown in the Australian registry [48], this difference in revision rates becomes more emphasised as the diameter of the bearings increase.

THR Metal Ion Concentrations, Wear and ARMD and Resurfacing Implants Comparisons

Reports of ARMD in the presence of optimally functioning implants are rare. However it does not follow that metal ion concentrations (and thus total volumetric wear) are dose related to the amount of tissue damage identified at revision surgery [3, 4]. Previously, ARMD has been divided into histiocyte-dominated (ARMD-H) and lymphocytic-dominated responses (ARMD-L) [3]. ARMD-L cases are often

found to have the greatest extent of soft tissue destruction. The implication is that soft tissue damage is caused by the immune response rather than a direct toxic effect of the locally elevated Cr and Co concentrations. It is this distinction which may ultimately prove to be the underlying explanation for the difference in clinical performance and failure modes of hip resurfacing and THR systems. It may also explain the confusion which reigns in the literature on the subject of whether blood tests are of any clinical use. It is interesting to note that when patients with resurfacings are analysed as a group on their own, authors tend to conclude that risk factors for failure are smaller joint sizes, suboptimally positioned acetabular components and elevated metal ion levels/increased wear [3, 49]. However, when studies examine THR patient groups (or actually combine THR and resurfacing patients into the same group), it is often concluded that ARMD is not related to size, orientation or elevated metal ion concentrations [50].

Failure rates of ASR, Durom (Zimmer, Warsaw, Indiana) and BHR THRs are greater than the failure rates of the pure resurfacing systems [51]. Furthermore, Garbuz et al. [52]. Nargol et al. [53] and Beaulé et al. [23] have shown evidence that median blood metal ion concentrations are elevated in THRs compared with their resurfacing counterparts in studies involving the Durom, ASR and Conserve Plus (Wright Medical, Memphis, Tennessee) systems, respectively. A recent prospective study in the United Kingdom comparing the BHR with the BHR THR was terminated due to unacceptably high metal ion levels in patients receiving the THRs [54]. There is something quite different happening with large-diameter MoM THRs. The difference is the taper junction [55].

Retrieval Analysis of Contemporary Large-Diameter Taper Junctions

Failing modular junctions show distinctive changes which are particularly marked on the female taper surface [56]. These changes correspond to the morphology of the trunnions with which they were coupled. The commonest pattern of surface change encountered presently is shown in Figs. 5.6 and 5.7. This pattern has been identified by this investigator on the internal surfaces of Smith and Nephew, DePuy and Zimmer products. This phenomenon appears to be more commonly reported in MoM systems, although it may be that other large-diameter THRs are at risk. The internal surface of the head taper shows surface changes which are mirror images of the machined surfaces of the mated trunnions. These appearances are consistent irrespective of whether the stem is Co–Cr or a titanium (Ti) alloy stem. A number of researchers have stated that these changes are due predominantly to a corrosive process [57, 58]. But examination of the surface changes makes this explanation, in my opinion, unlikely [56]. The confusion lies in the apparent paradox that the Ti alloy stems (which, by assumption should be 30 % softer than the Co–Cr alloy) remain initially intact while the harder Co–Cr alloy is eroded. Yet our recent examination of retrieved Ti alloy stems compared to equivalent sterile components, has shown that Ti alloy undergoes an oxidation process which hardens its surface in vivo. The Ti alloy appears to deprive the Co–Cr alloy of its own protective oxide layer. The Ti hardens

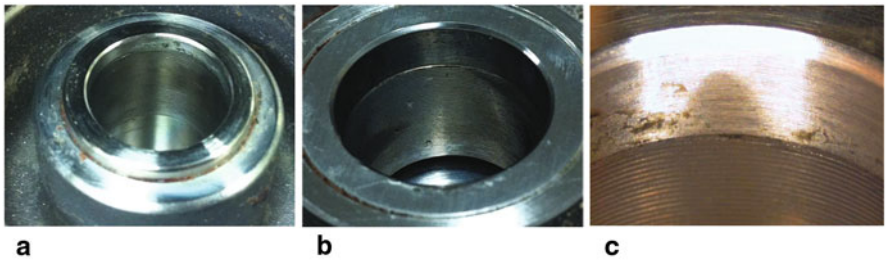

Fig. 5.6 **a** Internal taper surface of DePuy ASR XL head which was coupled with a Corail stem. **b** Birmingham Modular Head which had been coupled with a Synergy stem. **c** Magnified version of the transition zone of the ASR XL head. At the top of the picture the as-manufactured smooth surface can be easily differentiated from the trunnion imprint deeper down. In heavily worn cases this transition is palpable

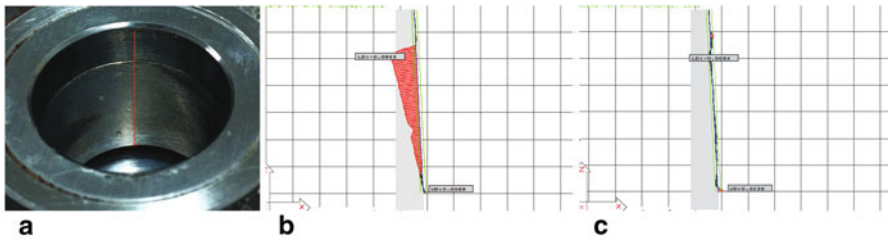

Fig. 5.7 **a** Direction of a linear trace taken with a coordinate measuring machine. **b** Resulting cross-sectional image through the side with maximal damage. The *green parallel lines* show the manufacturing tolerance bands of an idealised taper. There is a maximum wear depth here of 95.5 μm which corresponds to the engagement area of the base of the trunnion. **c** Resulting cross-sectional image through the side of the taper directly opposite that shown in **b**. Surface changes here are minimal. This one-sided damage is a typical finding in failed taper junctions

continually over time while the Co–Cr remains essentially in the as-manufactured form. Corrosion yes, but corrosion leading to wear, rather than the classic idea of fretting corrosion. The result: The Ti wears away the "softer" Co–Cr head. Exactly the same "imprinting" process occurs with Co–Cr trunnions [59]. This may be due to a work-hardening process of the Co–Cr trunnion when the grooves are manufactured into the surface. This is currently under investigation.

Taper Debris and Bearing Surface Debris—Different Clinical Consequences

Joint Fluid Metal Ion Ratios

There are a number of different clinical observations and consequences of taper debris when compared to bearing surface wear. The first quantifiable difference can

be seen in joint fluid Cr:Co ratios [60]. A failing taper junction in the absence of excess bearing surface wear tends to load the hip joint fluid with Co in preference to Cr ions. This difference may well be due to the fact that the Co–Cr taper surface cannot repassivate, and thus the bulk alloy is lost through tribocorrosive mechanisms. The very reverse is true with excessive bearing surface wear—the joint fluid Cr concentration is often more than three times that of the Co concentration and is not, uncommonly, five times greater. This difference in metal ion ratios can be a useful sign to differentiate between excessive bearing surface wear or failing tapers. It can alert the surgeon prior to revision surgery as to the need for consideration of a protective sleeve for the trunnion, if it is to be retained, or even for stem removal.

Taper Debris Appears to Have a Greater Clinical Impact

Our ongoing investigations are showing a clear difference between the clinical significance of an amount of material loss from a taper junction and an equivalent dose from the bearing surface. In a comparison of over 100 hip-resurfacing patients and 100 THR patients who have suffered significant tissue damage, the total Co–Cr volumetric material loss in the THR patients is 30 % of that in the resurfacing patients. Consistent with these findings, blood and serum Cr and Co concentrations in THR patients suffering ARMD are significantly lower. Frequently they are lower than the 7 μg/L threshold level suggested by the MHRA. This relationship has been noted by a number of authors [53, 61]. It may also be the reason why one study found that the wear rates of failed ASR devices (a device widely acknowledged to have very poor clinical performance) were not found to be significantly different to the wear rates of BHRs. Examining the breakdown of explants in this study revealed something quite interesting: The ASR explants were split roughly with 2:1 ASR THRs to ASR resurfacings and 1:2 BHR THRs to BHRs. The same authors also found that pseudotumours are common in well positioned, low-wearing devices. There was no mention in either study of the taper junctions [62, 63].

Given that, as discussed above, soft tissue destruction does not appear to be directly linearly related to wear rates/metal ion concentrations but rather to a negative immune cascade once a threshold has been passed, it is not unreasonable to suggest that taper debris is more immunogenic.

1. Acceleration of debris production rather than total dose or average wear rate may be more significant in the development of the host response. When tapers begin to fail, the acceleration in debris production may be far steeper than in a failing bearing surface.
2. Potential synergy effects of Co–Cr alloy with Ti alloy debris which is another critical research area [64].
3. The ratio in which Co and Cr ions are released may play an important role. For example, higher localised concentrations of Cr as seen in excessive surface wear may alter the capacity of lymphocytes.

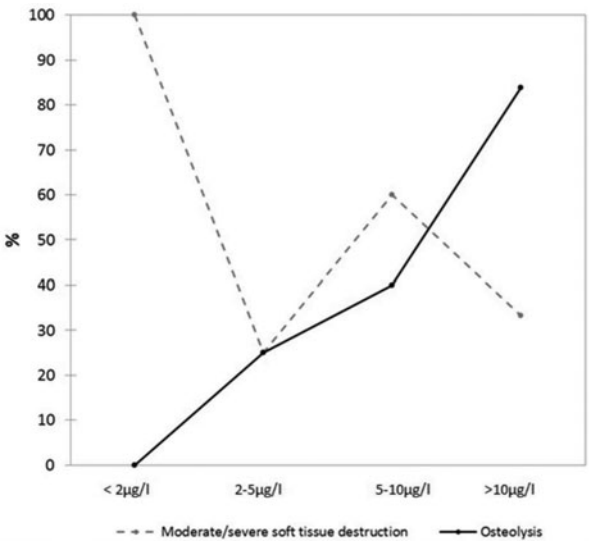

Fig. 5.8 The incidence of osteolysis and or moderate/severe soft tissue destruction at revision surgery in the patients described in the asymptomatic ions study. Patients have been grouped according to their pre-operative blood result

4. The location of debris production. Firstly, synovial fluid may have an important buffering effect on the released debris. Furthermore with uncemented stems, debris liberated from the taper junction may find a route to the bone marrow, again with differing immunogenic potential.
5. Taper debris may be an association rather than a root cause. For example it has been suggested that fluid ejected when head and cup components separate and relocate has an important role in the development of tissue necrosis [65]. This mechanism may simply be more frequent in THRs compared to resurfacings.
6. Finally, and in my opinion the most likely explanation, may be a difference in particle size of taper debris compared to surface debris. This is another important avenue of future research. (Fig. 5.8).

Irrespective of the underlying mechanisms, large-diameter MoM THRs are failing at a higher rate than their resurfacing counterparts. The ASR THR has been described as having a failure rate as much as 44 % at 7 years [48]. I have personally examined 120 failed ASR THRs. In my opinion, taper failure has occurred in over 60 % of these cases. The extent of taper damage is not clearly linked to surface wear—the implication being that there is no reason at present to say without doubt that this is uniquely an ASR problem.

Most importantly, at present, Co and Cr blood levels, unless they are within the ranges of physiological values described herein (< 2 µg/L), are of no real use for these arthroplasty systems in terms of identifying pathological responses. All patients with these devices must be kept under strict follow up until we know more.

Summary

Blood metal ion testing is a useful adjunct in the management of MoM hip arthroplasty patients.

Blood Co in particular is an excellent surrogate indicator of the tribological performance of MoM bearing surfaces. In the United Kingdom experience, a level of 5 μg/L can be considered with confidence to be associated with a joint that is wearing at an accelerated rate.

Confirmed Co or Cr serum or whole blood concentrations in excess of 20 μg/L are highly abnormal and the risk of progressive osteolysis should be considered high, even in the absence of pain.

Blood Co concentrations less than 2 μg/L, particularly in male patients with resurfacings, are associated with a low risk of ARMD.

Abnormal bearing surface wear places patients at greater risk of soft tissue damage although the extent of damage does not appear to be linearly related to wear or metal ion concentrations. This relationship is contrary to the risk of osteolysis, which appears to increase as metal ion concentrations increase.

Taper wear debris appears to be more likely to stimulate a lymphocyte-dominated response per unit of debris when compared to an equivalent dose of surface debris. Correspondingly, ARMD is more common in MoM THR patients and metal ion concentrations are less reliable. This important trend will require more clinical studies and scientific investigations of tapers, taper debris, wear debris, associated corrosion and local biological responses with studied comparisons and interactions.

Co concentrations in excess of Cr ion concentrations in hip fluid may be highly suggestive of taper damage.

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Chapter 6
Metal Sensitivity: Is It Possible to Determine Clinically?

Nadim J. Hallab and Paul H. Wooley

Introduction

Is it possible to determine metal sensitivity responses clinically? The simple answer to this question is yes, but the caveats are many and complicated, as will be discussed in this chapter. Excessive reactivity to metal implant debris or hypersensitivity to implant debris is relatively rare, where it is estimated that only 1–3 % of aseptic failures are due to hypersensitivity responses among traditional metal-on-polymer type total joint replacement designs [1–3]. Implants themselves are not known to cause hypersensitivity. Rather, implant debris (particles and ions) emanating from implant surfaces that have vastly different properties (e.g. metal ion release kinetics, specific surface areas, sizes, etc.) facilitate interaction with immune cells and elicit an immune response. This distinction is important, because when metal debris is minimized, the chances of metal hypersensitivity is also minimized [4].

This hypersensitivity is characterized by cell-mediated adaptive immune responses where conditioned lymphocytes respond to specific stimuli, as opposed to the more typical and less-specific response of macrophages to implant debris [5–7]. The slow progressive particle-induced osteolysis or "particle disease" generally refers to the process of peri-implant osteolysis, where implant loosening and inflammation are in main part due to implant particulate debris non-specifically interacting with innate immune system cells (i.e. tissue macrophages termed histiocytes) that occurs over many years (> 7 years) [8, 9]. In contrast, "metal sensitivity" or hypersensitivity has been predominantly characterized as specific, and increases in the prevalence of

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delayed type hypersensitivity (DTH) responses have been associated with the failures within the first 2–5 years from implantation of certain types of metal-on-metal (MoM) bearing implants as detected by unusual lymphocyte associated peri-implant responses and diagnostic immune metal-reactivity testing [2, 10].

To a large extent, implant materials and metals currently in use have evolved over time to the more successful candidates that wear and corrode to the smallest degree possible. Despite this optimization process, metal sensitivity is still well reported in both case and group studies [11–13]. How and why this occurs remains largely unknown. What is known is that all implant metals degrade by both corrosion and/or wear in vivo [14, 15] and the released debris (particles and ions) immediately are coated or complex with plasma proteins and interact locally and systemically [16, 17]. Released metal ions become antigenic by becoming haptens which activate the immune system by forming complexes with native serum proteins and altering their natural conformational structure [18–21]. These metal-altered-self-protein complexes are processed by antigen-presenting cells (APCs) and are recognized as foreign by lymphocytes that then become the hypersensitivity responses.

In its broadest definition metal sensitivity to implants is any aseptic (non-bacterial) material-driven "excessive" immune response that causes peri-implant pathology, such as bone loss or local inflammation of T-cells, B-cells or macrophages. The hotly debated aspect of this is just what constitutes "excessive". When an implant fails prematurely (< 7 years) due to an exuberant cell-mediated immune response to the same amount of implant debris that is typically well tolerated by most people, that response can be categorized as "metal-allergy", "implant-allergy", "implant sensitivity" or "hypersensitivity" [22]. The allergy/sensitivity/hypersensitivity terms have been liberally used as interchangeable in immunology and orthopedics despite specific nuanced differences between them. For simplicity within this discussion of metal sensitivity, any nuanced differences between them will not be discussed here.

Skin or dermal sensitivity to metals has been reported to cause skin hives, eczema, redness and itching, that affects approximately 10–15 % of people [11, 12, 21, 23–25] (Fig. 6.1), where hypersensitivity to nickel is the most common (approximately 14 %) [11], followed by cobalt and chromium [11, 21]. Other sensitizing metals include beryllium [26], nickel [23–26], cobalt [26] and chromium [26], and to a lesser degree tantalum [27], titanium [28, 29] and vanadium [27]. Although much still remains unknown about these biological steps and responses, this chapter will present an overview about what is known about how these metals elicit sensitivity in patients with implants.

Metal Sensitivity Mechanism

In general, hypersensitivity responses can take one of two central forms: (1) a humoral immediate (within minutes) type of response that is initiated by antibody–antigen complexes of Types I, II and III reactions, or (2) a cell-mediated delayed (hours to days) type of response [30, 31]. The metal hypersensitivity reactions currently

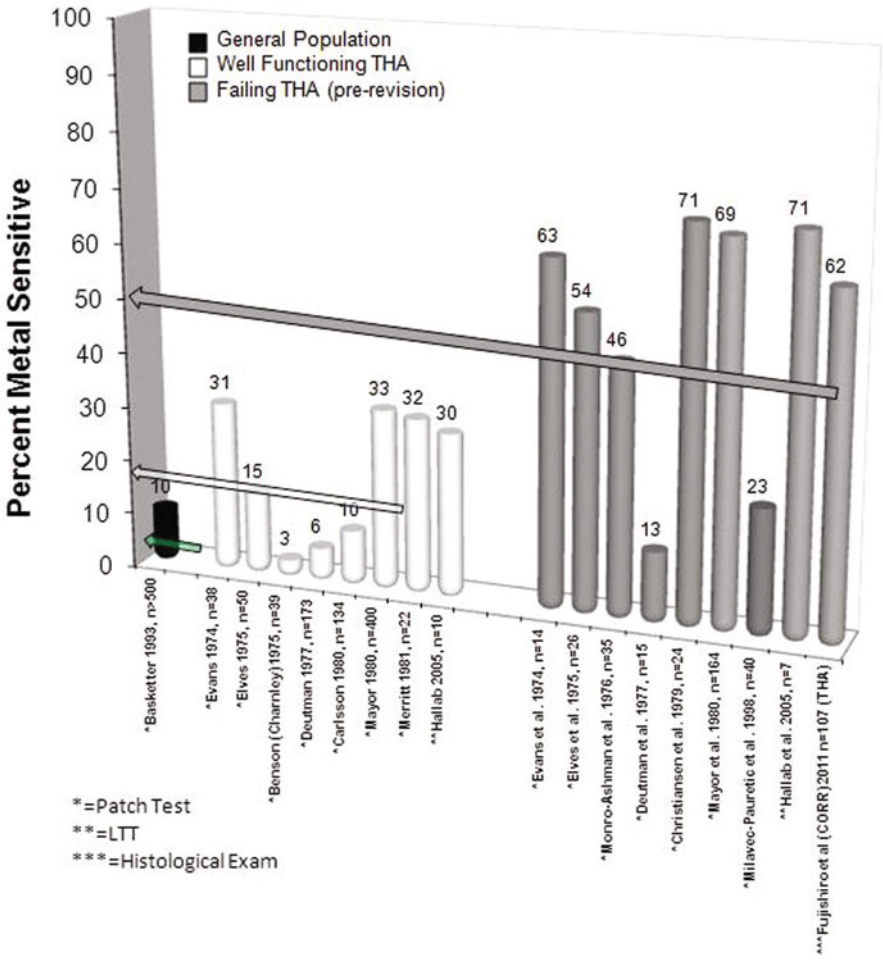

Fig. 6.1 A compilation of investigations show the averaged percentages of metal sensitivity among the general population for nickel, cobalt and chromium, among patients after receiving a metal-containing implant, and among patient populations with failed implants. All subjects were tested by means of a patch test, metal lymphocyte transformation test (LTT) or histological diagnosis

recognized are almost exclusively delayed type responses mediated by antigen-activated lymphocytes that have been classically categorized as Type IV Delayed Type Hypersensitivity responses (DTH).

This specific cell-mediated delayed type of hypersensitivity response is characterized by T-helper lymphocytes of the T_H1 subset. These T_H1 cells release a unique pattern of inflammatory cytokines, including interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin-2 (IL-2). Although these T_{H-1} cells are needed to combat intracellular pathogens, T_{H-1} when they are erroneously released and activated can result in autoimmune diseases [32, 33].

In this fashion, metal-sensitized and activated T-cells, in conjunction with primed/recruited APC's, will secrete a variety of pro-inflammatory cytokines that recruit and activate other innate immune cells, e.g. macrophages, monocytes and neutrophils [22]. These signature cytokines include IFN-γ and TNF-β which, of the many pro-inflammatory effects on local cells (e.g. endothelial cell), induce migration inhibitory factor (MIF)—which prevents the migration of recruited macrophages away from the site of the metal-DTH reaction (see Table 6.1). The hallmarks of a DTH response are infiltration, activation and eventual migration inhibition of innate immune cells (e.g. macrophages). These recruited and activated macrophages have an increased ability to phagocytize, process and then present pieces of the phagocytized metal–protein complexes (immune epitopes) on their surface for T-cell recognition (in class II Major Histocompatibility complexes (MHCs) for interaction with T-cell receptors (TCRs)). The release of cytokines from the recruited APCs (such as IL-1), can trigger the recruitment/activation of more T-cells, which in turn activates more macrophages in a vicious cycle. Under certain circumstances, and in some auto-immune diseases where there is an inability to turn off this DTH self-perpetuating response, the runaway results can be extensive tissue damage. Thus, the current strategies to mitigate these types of responses in people are geared towards immunosuppressive therapies that clip or temporarily stop this vicious cycle and allows the response to abate [34, 35].

However, targeted therapy for selected immunosuppressive therapies has not been developed yet due to the many things that remain unknown about metal sensitivity, including (1) how to address the fact that different specific lymphocyte populations are activated in different individuals [36], (2) the specific cellular mechanisms of recognition and activation and (3) how serum metal–protein complexes become antigenic. Dermal sensitivity is more easily studied and thus dermal metal allergy has been better characterized to some extent [37]. Skin is the primary immune barrier and the APCs of the skin, Langerhans cells, are exquisitely good at gathering and presenting antigen. Each dendritic Langerhans cell is responsible for the immuno-surveillance of 53 epidermal cells, in an amazing consistency from person to person [38]. Unfortunately these cells differ in several ways from the APC's in the periprosthetic region. Peri-implant APCs include macrophages, endothelial cells, lymphocytes, dendritic cells and, to lesser extent, parenchymal tissue cells. Tissue macrophages (histiocytes) are considered the primary APCs around implants and are involved in implant debris phagocytosis. The highly variable regions of TCRs that recognize the metal–protein complex presented by APCs have been widely acknowledged as central to metal sensitivity [39, 40, 41]. To complicate matters, metals such as nickel have also been shown to act in both classical and non-traditional ways to activate T-cells, one of which is to simply cross-link TCRs and co-stimulatory receptors on T-cells (e.g. VB17 of CDR1 TCR) to create what is termed a "superantigen" activation of TCRs [40, 42]. Despite the identification of ways by which non-typical metal induced lymphocyte activation can occur, the traditional DTH response remains the dominant mechanism associated with implant-related hypersensitivity responses [43–45], where one group of clonally specific/sensitized lymphocytes respond to metal challenge.

Table 6.1 Selection of important cytokine involved in innate and adaptive immune responses to implant debris (source and mechanisms of action) [6, 32–34, 125]

Cytokine	Principle source	Principal activities
Macrophages (innate immunity)		
IL-1β	Macrophages/monocytes	T, B-cell activation; pro-inflammation
TNFα	Macrophages, TH-1 cells	Pro-Inflammation; tumor killing
MCP-1	Monocytes, endothelial cells	Chemotactic for monocytes but not neutrophils
IL-1ra	Macrophage/monocytes	IL-1 receptor antagonist blocks action of IL-1
IL-6	Macrophages, T cells	B cell stimulation, inflammation
IL-8	Macrophages	Meutrophil (PMN) attraction
IL-12	All APCs	Stimulates T-cells into Th1-cells and IFN-g
IL-18	Macrophages/monocytes	Stimulates IFN-gamma production
GM-CSF	Macrophages/T-cells	Proliferation/differentiation macrophages
Lymphocytes (adaptive immunity)		
IFNγ	T-cells, macrophages	Inflammation, activates macrophages (induces Th1)
IL-2	T-cells	Inflammation, activates macrophages (induces Th1)
IL-4	T-cells	Inflammation, activates macrophages (induces Th2)
IL-10	Th2 and macrophages	Inhibits Th1 cytokines, enhances B-cells survival/proliferation, and can block NF-κB

Testing for Metal Sensitivity

Currently approved methods for human diagnostic testing for metal allergy include both skin testing (patch testing) and in vitro blood testing using LTT. There are commercially available assays for physicians that contain some of the metals in orthopedic implants [30, 46].

Dermal Testing While general patch testing protocols and commercial kits do exist for a variety of common metals [30, 46] there are questions regarding the applicability of skin testing to diagnose in vivo immune responses to orthopedic implant debris. In particular, there are questions regarding the location-specific APCs and skin vs serum challenge of metal challenge agents [1, 18–20]. It is hard to imagine that the exquisite specificity of myriad immune responses are not dramatically affected by both the haptenic potential of metals in a dermal environment (in which dermal Langerhans cells are the primary effector cells) vs that of an in vivo closed peri-implant environment [31, 47]. This difference is highlighted by the amazing APC's of the skin, where unique antigen-processing/endosomal-recycling organelles, called Birbeck granules, are present in Langerhans cells but are not found in the dominant

peri-implant APCs such as macrophages [48, 49]. There are other important limitations to dermal testing for implant-related metal sensitivity including the following: (1) The rudimentary and relatively subjective nature involved with grading a dermal reaction from 0 to + 3 which precludes detection of more subtle but statistically significant group differences and incorporates the wildly different opinions of clinicians on what constitutes a + 1, + 2 or + 3 response. (2) Dermal testing may be affected by site-specific immunological tolerance (i.e. suppressed skin reactivity to implants) [46, 50]. (3) There may be impaired host immune responses that are genetic, or environmental, e.g. concurrent medications [51, 52]. (4) The biggest risk associated with patch testing is the possible sensitization of metal sensitivity in a previously non-sensitive individual [53]. (5) The conditions of immune challenge during patch testing are also highly variable (i.e. non-standardized), where the environment of a patch test placed on a hairless area of the skin (typically the upper back) for 48–72 h is highly inconsistent from patient to patient and uncomfortable, where such aspects as cleanliness of the area and home environment is not standard. (6) Finally, there are no well-established challenge concentrations/doses and methods for several orthopedic metals available in commercially available/approved patch test kits (e.g. Al, Mo, V and Zr, Table 6.2).

Lymphocyte Transformation Testing Less risky from an induction perspective is LTT, which measures the proliferative responses of blood drawn lymphocytes after they are exposed to specific antigens or haptens for 3–6 days. These lymphocytes are obtained from a regular blood draw where the mononuclear cell fraction is isolated after centrifuging the heparinized blood on a layer of Ficoll (density gradient separation). Proliferation is measured using a radioactive marker and is added to cultured lymphocytes with challenge agents. The incorporation of radioactive [^{3}H]-thymidine into cellular DNA upon mitosis facilitates the quantification of a proliferation response through the measurement of incorporated radioactivity after a set time period, typically after 5–6 days of challenge (with 0.001–0.1 mM Al^{+3}, Co^{+2}, Cr^{+3}, Mo^{+5}, Ni^{+2}, V^{+3} and Zr^{+4} chloride solutions). During the last day of 12–24 h of antigen exposure, radiolabeled [^{3}H]-thymidine treatment is used to measure proliferation by measuring the amount to which it is incorporated into dividing cells DNA after "harvesting" (collecting) cells onto a paper membrane and then using liquid scintillation measurement of radiation counts per minute (cpm). This method of measuring cell proliferation is highly precise because of the ability to measure a small subset of antigen-activated dividing cells amongst the many other in a culture well, due to incorporation of radioactive Thymidine into cell DNA upon mitosis. A proliferation or stimulation index is calculated:

Proliferation Index (Factor) = (mean cpm with treatment)/(mean cpm without treatment).

The use of LTT in the assessment of orthopedic implant-related metal sensitivity is growing and although less popular and less available than patch testing (due to the highly complex nature of the immune test: culturing, challenging and measuring proliferation), it has been well established as a method for testing hyper-sensitivity in a variety of clinical settings [54–59]. Some reports seem to indicate LTT may

Table 6.2 The percentages of metals in different orthopedic alloys

Alloy	Ni	N	Co	Cr	Ti	Mo	Al	Fe	Mn	Cu	W	C	Si	V
Stainless steel (ASTM F138)	10–15.5	< 0.5	< 0.05	17–19	< 0.05	2–4	< 0.05	61–68	< 0.05	< 0.5	< 2.0	< 0.06	< 1.0	< 0.05
CoCrMo alloys														
(ASTM F75)	< 2.0	< 0.05	61–66	27–30	< 0.05	4.5–7.0	< 0.05	< 1.5	< 1.0	< 0.05	< 0.05	< 0.35	< 1.0	< 0.05
(ASTM F90)	9–11	< 0.05	46–51	19–20	< 0.05	< 0.05	< 0.05	< 3.0	< 2.5	< 0.05	14–16	< 0.15	< 1.0	< 0.05
(ASTM F562)	33–37	< 0.05	35	19–21	< 1	9.0–11	< 0.05	< 1	< 0.15	< 0.05	< 0.05	< 0.05	< 0.15	< 0.05
Ti alloys														
CPTi (ASTM F67)	< 0.05	< 0.05	< 0.05	< 0.05	99	< 0.05	< 0.05	0.2–0.5	< 0.05	< 0.05	< 0.05	< 0.1	< 0.05	< 0.05
Ti-6Al-4V (ASTM F136)	< 0.05	< 0.05	< 0.05	< 0.05	89–91	< 0.05	5.5–6.5	< 0.05	< 0.05	< 0.05	< 0.05	< 0.08	< 0.05	3.5–4.5
45TiNi	55	< 0.05	< 0.05	< 0.05	45	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
Zr alloy (95 % Zr, 5 % Nb)	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

Alloy compositions are standardized by the American Society for Testing and Materials (ASTM vol. 13.01)

be equally or better suited for the testing of implant-related sensitivity than dermal patch testing [55]. Other investigations show that metal sensitivity can be more readily detected by LTT than by dermal patch testing [60–62]. This increased sensitivity (minimized false negative) may be more important than high specificity (minimized false positives). Why? Because there is a choice of commercially available implants made from different metals and these different implants are generally equally successful, thus it is more important to be able to determine everyone who has metal sensitivity (at the expense of some false positives) because the risk of choosing a different better appropriate implant material carries little to no risk. In comparison missing the diagnosis of metal sensitivity for better specificity (minimized false positives) carries with it the spector of early failure and revision surgery for the patient.

One potential benefit of metal LTT is the use of mixed mononuclear cells derived from a blood draw (i.e. T-cells, B-cells and other more rare lymphocyte populations) that are directly exposed to metal challenge and thus may more closely mimic that of the local implant environment (compared to the dermal metal challenge). Additionally, soluble metal chloride challenge agents are able to complex with serum proteins from the same individual that is tested, i.e. autologous serum [63–65]. These artificially created metal–protein challenge agents have been shown to be similar to those produced in vivo [17, 66, 67]. However, the precise metal–protein complexes that are produced on and in the dermal tissue remain uncharacterized [17, 22]. LTT is also both highly quantitative and not technician/operator dependant (vs patch testing) [2]. A quantitative stimulation index is produced from multi-well replicates that enables calculation of an average and standard deviation for each metal challenge agent at each concentration. This increased sampling size enables the study of different patient cohorts, metal challenge agents, dose responses, different implant types, etc. An advantage of LTT over dermal testing of metal coupons is the ability to test several known concentrations (dose responses) for each metal agent (e.g. > 10) at (e.g. 0.01, 0.1 and 0.5 mM). Most immune responses are dose dependent especially in individual patients. Too little or too much immune challenge may not induce a response or simply induce toxicity, respectively. Thus, using different challenge doses is of central importance for current LTT. This provides a means to assess those people who are sensitive at lower than normal (e.g. 0.01 mM) or higher than normal (e.g. 1 mM) challenge concentrations of metal challenge. This scenario is illustrated in Fig. 6.2 where LTT results of a metal sensitive individual demonstrate dose dependent increased reactivity to Ni. Additionally advantageous is that LTT has reported greater sensitivity than dermal patch testing [62, 68–72]. While this greater sensitivity may increase the likelihood of false positives (decreased specificity), it more importantly minimizes the occurrence of false negatives, which in the authors' opinion, as stated earlier, is in the best interests of the patient, given the little to no additional risk of choosing a more biologically suited implant material for the patient. This testing is gaining popularity and is more relevant than ever, due to the increasing numbers of implants going into patients and the increasing numbers of surgeons [73] that have the technical ability and expertise to put in different implants that are made of different alloys (e.g. titanium alloy vs cobalt alloy vs zirconium alloy).

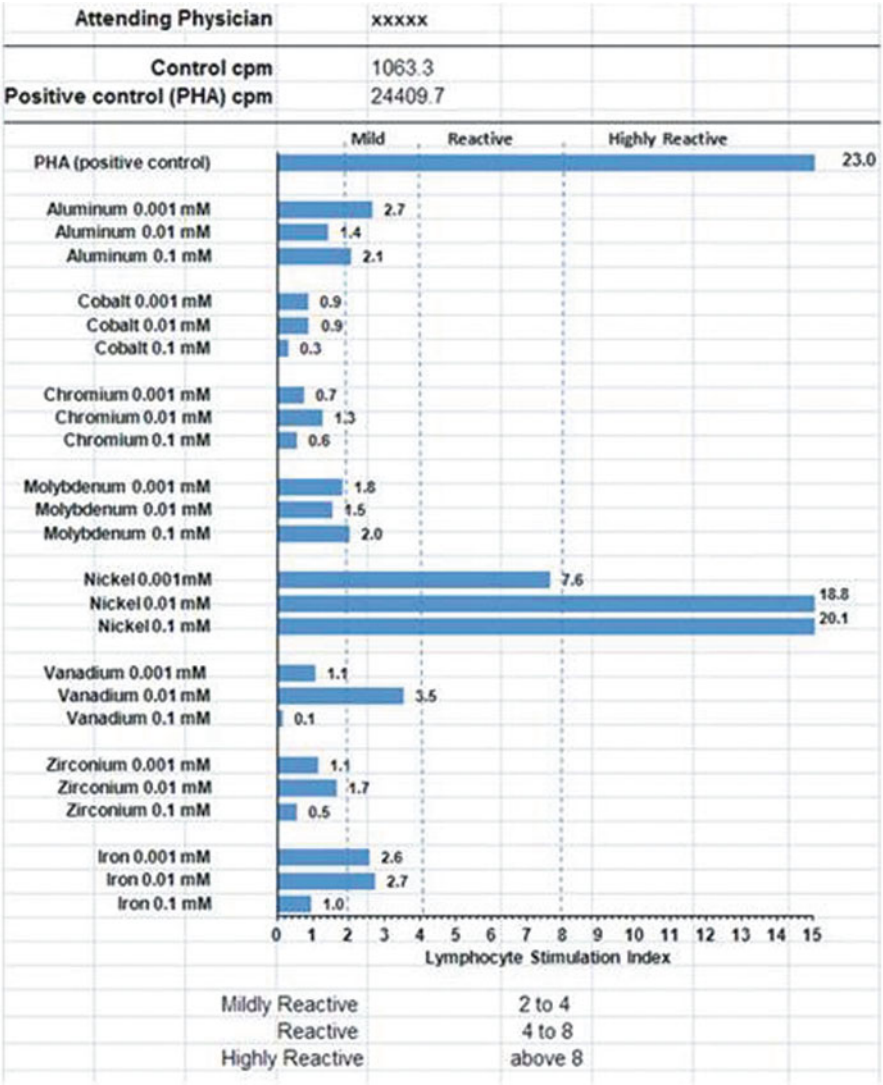

Fig. 6.2 Sample results of a metal LTT indicate high reactivity to Nickel at all 3 concentrations tested. Metals are generally used at 3 different concentrations of 0.001, 0.01 and 0.1 mM. (Courtesy of Orthopedic Analysis LLC)

Contemporary LTT does still require more enhancements. Metal solutions allowed to complex with proteins only approximate the kinds of products generated by corrosion and wear during metal implant degradation [17, 65, 67], and the degree to which lymphocyte reactivity is affected by any subtle differences remains unanswered. Additionally, it is unclear what the lower bound of stimulation index number (i.e. threshold) best indicates a clinically relevant hypersensitivity response. In the

past our laboratory and others have used an experience-based criteria of a stimulation index threshold of > 2 ($p < 0.05$) to indicate mild metal hypersensitivity and > 8 to indicate severe metal reactivity, consistent with drug allergy literature over the last half century [39, 56, 62, 74, 75]. However, it remains unclear from these studies whether this criterion is too strict or too permissive.

More prospective, longitudinal clinical studies, such as the metal-on-metal study discussed in the following section, provide support to why LTT and patch testing are meaningful in a clinical setting even with needed enhancements. Specific types of implants with greater propensity to release allergenic metals in vivo may be more prone to induce metal sensitivity. For example, failures of total hip prostheses with MoM bearing surfaces have been associated with greater prevalence of metal sensitivity than similar designs with metal-on-ultrahigh-molecular-weight-polyethylene bearing surfaces [50, 76]. Many case and group studies indicate the clinical utility and expansion of metal sensitivity testing for total implant recipients [2, 3, 22, 77–80].

Case Studies in Metal Implant-Related Metal Sensitivity

Many reports over the past 40 years have implicated metal allergy or sensitivity type responses, where the release of implant debris was temporally connected to specific responses such as severe dermatitis, urticaria, vasculitis [81–86] and/or non-specific immune suppression [51, 87–90].

One of the first correlations of dermal metal reactions to the poor performance of a metallic orthopedic implants was made in 1966 by Foussereau and Lauggier [91] where a nickel-containing implant was accompanied by dermal hypersensitivity reactions. There have been many case reports over the past 40 years that link immune responses with adverse performance of metal implants in the cardiovascular [85, 92, 93], orthopedic [12, 81, 83, 84, 86, 94], plastic surgery [95] and dental [96–102] fields. In many instances, excessive early immunological reactions (aseptic inflammation) have necessitated device removal, and after explantation the immune reactions dissipate [81–86]. Sometimes (but not always) severe skin reactions [82, 84, 85, 92–94, 103, 104] accompany the aseptic inflammation and they have also been reported to appear in conjunction with the relatively more general phenomena of metallosis (dark metallic staining of tissue due to excessive implant debris), excessive periprosthetic fibrosis and muscular necrosis [86, 105, 106].

This dermal reaction was true in one of the earliest cases of metal implant sensitivity [83], where a 20-year-old woman had symptoms of inflammation including rashes on her chest and back, approximately 5 months after stainless steel screws were used to treat chronic patellar dislocation. Topical steroids worked to treat this condition for 1 year, after which it worsened with more generalized dermal eczema, until the implant was removed. After the stainless steel screws were removed her dermal rashes completely disappeared within 72 h [83]. “The orthopedist still doubted that the steel screws could be the cause of her dermatitis and applied a stainless steel

screw to the skin of her back. In a period of 4 h, generalized puritus and erythema developed" [83]. Dermal patch testing showed aggressive reactions to nickel and the steel screw. What is fascinating about this early case is that it satisfies Koch's Postulates, a key test for causality in medicine. An agent can be considered as causative when it is removed and the symptoms abate, and when it is returned the symptoms also return. Thus, metal sensitivity associated with implant materials was conclusively demonstrated nearly 40 years ago, albeit only in a case study. There were a number of case studies to follow that showed similar temporal and physical evidence of delayed type hypersensitivity response reactivity to orthopedic implant metals [12, 21, 81, 84, 86, 95].

Generally, among the literature there are more cases of metal sensitivity reported to stainless steel and cobalt alloy implant induced immune responses and less to titanium alloy components [12, 21, 81, 82, 84, 93, 94, 104, 107, 108]. One of these early case reports of cobalt metal sensitivity indicated that metal sensitivity type responses including periprosthetic fibrosis, patchy muscular necrosis and chronic inflammatory changes peripherally, occurred 7 years after the initial operation of cobalt alloy plates and screws used in the fracture fixation of a 45-year-old woman's left radius and ulna [43]. This patient's response demonstrated that the time to develop this kind of response is not limited to the first few years of implantation. And after the implant was removed and the symptoms (swelling) disappeared, the patient remained reactive to cobalt as indicated by patch testing [43].

Cohort Studies of Implant-Related Metal Sensitivity

Almost the entire bulk of the evidence attesting to the clinical utility of metal sensitivity testing can be attributed to the many retrospective cohort studies that indicate a strong correlation between metal exposure and the performance of a metal-containing implant and metal sensitivity [12, 46, 50, 109–117]. These studies show that the incidence of metal sensitivity among patients with elevated metal exposure with well-functioning implants is approximately 25 %, roughly twice as high as that of the general population (Fig. 6.1) [46, 50, 76, 108, 110, 112, 113, 116, 118]. This sensitivity dramatically increases to 60 % in patients with a painful or poorly functioning implant (as judged by a variety of criteria) [76, 108, 110, 112, 118]. While current evidence suggests otherwise [22, 78], these patients may be "selected" for failure due to a pre-existing metal allergy. Thus the incidence of metal sensitivity in people with painful/failing implants is about six times that of the general population and approximately more than two times that of people with pain-free well performing implants [119].

Evident from past and current group studies is that specific types of implants that release more metal ions and/or particles are more likely to induce metal sensitivity [22, 78]. Some MoM total hip prostheses designs and some surgical placement resulted in metal sensitivity to a greater extent than similar designs with metal-on-ultrahigh-molecular-weight-polyethylene bearing surfaces [22, 50, 76]. New

generations of metal-on-metal (MoM) total hip replacements generally have the advantage of lower overall wear than metal-on-polymer implants but release more metal ions and particles and have greater reports of failures attributable to excessive inflammatory reactions. Hypersensitivity-like reactions have been reported to be as high as 76–100 % of the people with failing MoM implants [120, 121]. These sensitivity responses include histological inflammation accompanied by extensive lymphocyte infiltrates [120, 121]. Recent prospective studies involving people with MoM implants showed that at least over the short term, in vivo metal sensitivity responses develop even in asymptomatic well-performing MoM implants [22]. One study reported a significant increase in metal sensitivity from 5 % pre-op to 56 % at 1–4 years post-op in people with well-performing (asymptomatic) MoM surface replacement hip arthroplasties [22]. Within the same investigation, a retrospective analysis of people with asymptomatic MoM implants in place for longer than the prospectively studies group (i.e. > 7 years on average) had an even higher average incidence of metal sensitivity at 76 %, presumably because the implants were in longer exposure to elevated levels of metal (2–11 years). These levels, while high, are less than those previously reported for painful/symptomatic MoM patients (i.e. 81 % in failing MoM implants by Thomas et al. [2]). While a pattern of increasing metal reactivity with implantation time supports a causal or contributing relationship between local adaptive immune responses and the pathogenesis of MoM failure, it may be argued that the generation of wear from a failing bearing results in an immunological response to metal/protein complexes unrelated to the pathology of the implant failure . However, regardless of the role of the immune response in implant failure (which may not be generalized to individual patients) the overall findings of recent studies [22, 78] support the use of sensitivity testing for assessing implant performance. We found that [22] lymphocyte sensitivity responses to Co and Cr were not apparent at 3 months post-operatively (when serum levels of metal were already high), but developed after 1–4 years, Fig. 6.3. However, this “slow” increase in reactivity contrasted with the relatively fast elevations in Co and Cr metal ion levels measured at 3 months post-operatively. This delay suggests that metal sensitivity responses to this type of implant may develop over time and may be related to metal ion exposure levels. Incidentally, in this same study, patch testing did not correlate at any time point with in vivo metal ion levels or other measures of metal-induced immune responses such as metal LTT, flow cytometry or cytokine analysis. This study finding also suggests that patch testing may not adequately reflect adaptive immune responses in the local implant environment.

Other studies have also shown elevated levels of circulating metal ions correspond to increased acquired metal sensitivity responses and other specific MoM pathologies. Kwon et al reported that people with MoM hip implants and radiographically identifiable pseudotumors had a nearly two times increase (80 vs 45 %) in incidence of metal reactivity to Ni (LTT, SI > 2) and had fivefold increases in both Co and Cr serum ion levels, when compared to people with MoM implants without non-pseudotumors [77]. We have reported in a current large study of pain levels compared to metal sensitivity levels in people with various orthopedic hip arthroplasty implants that the percentage of people metal sensitive (metal LTT with SI > 2) was significantly higher for people with more painful implants vs non-painful (Fig. 6.4)

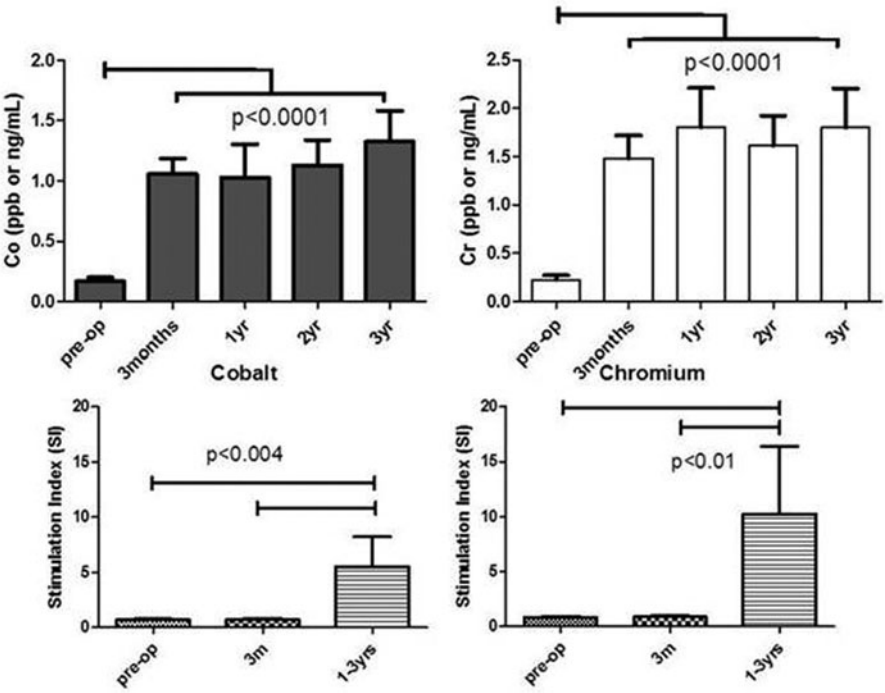

Fig. 6.3 Metal ion levels of Cobalt and Chromium are shown increased as early as 3 months in serum in people with metal-on-metal hip arthroplasty implants. However, increases in metal reactivity as measured by lymphocyte proliferations (*SI*), were only increased after 1–3 years of metal exposure in the same people with metal-on-metal hip arthroplasties. All people with metal implants used in this study were assymptomatic ($n = 21$, $p < 0.04$, Mann Whitney). (Adapted from Hallab et al. [22])

[119]. Furthermore, when the levels of metal-induced lymphocyte reactivity were categorically compared based on mild ($2 < SI < 4$), moderate ($4 < SI < 8$) or high ($SI > 8$) sensitivity with self-reported mild, moderate and high pain levels, they were significant different in pain levels between people with moderate vs high sensitivity levels. Conversely, people with Total Joint Arthroplasty (TJA) and no pain or low pain levels demonstrated a relatively low incidence of metal sensitivity (not significantly different, Fig. 6.4). This correlation suggests that pain may be connected to lymphocyte-associated immune reactivity to metal implant degradation products where higher self-reported pain levels can correlate with higher incidences of metal reactivity in vitro.

Clinical Relevance

All these past and recent studies illustrate the clinical need for sensitivity testing for two sets of people: (1) patients with a known history of metal sensitivity, and (2) patients with a painful implant where infection has not been detected through multiple

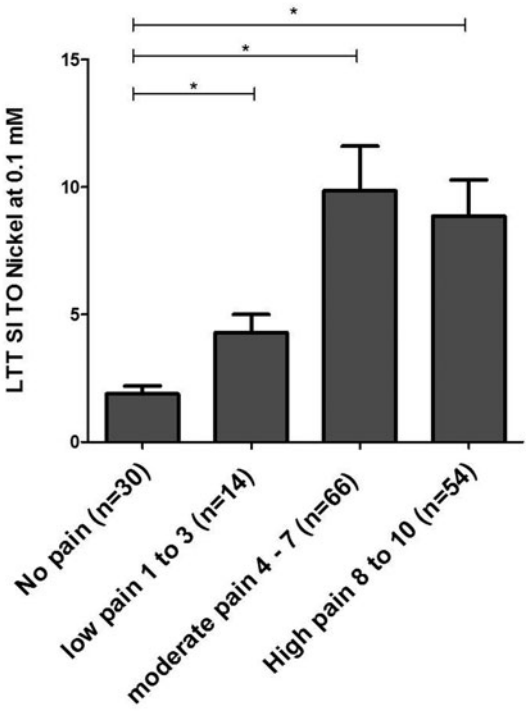

Fig. 6.4 Incidence of Nickel reactive subjects (*LTT*) according to self-reported pain levels in patients with no history of any allergy at a challenge concentration of 0.01 mM. Nickel reactivity in TJA subjects was based on their lymphocyte *SI* and was categorized as follows. Pain levels were denoted as follows in a scale of 1–10: *no pain* (0), *mild pain* (1–3), *moderate pain* (4–7), *high pain* (8–10). To obtain the incidence of metal reactivity, the percentage of subjects non-reactive, mildly reactive, reactive and highly reactive to Nickel at 0.01 mM concentration were calculated within their respective pain level group: *no pain* ($n = 30$), *mild pain* ($n = 14$), *moderate pain* ($n = 66$), *high pain* ($n = 54$). (Courtesy of Orthopedic Analysis LLC)

approaches. Although the evidence remains indirect, metal sensitivity testing is a direct measure of immune cell reactivity to implant metals, and thus represents real and heightened immune reactivity (and not simply a correlative biomarker with unknown role in the pathology). Immune reactivity to metal is well established as associated with implant performance and thus it is likely that a detectable, reproducible and quantifiable elevated immune response to an implant metal represents a clinically important phenomenon. Metal sensitivity testing is a direct test of an individual's immune response to metal challenge and the results indicate levels of immune reactivity that have been used for the past half century to measure delayed type responses drugs (such as antibiotics) and the persistence/effectiveness of vaccines such as tetanus toxin [122, 123]. Thus, it is highly likely, once a sensitivity response to metals is initiated (either before or during implant loosening or failure), that response directly plays into the etiology of further implant failure. Thus, the question of whether metal sensitivity initiates the pain, loosening, etc., is less important once sensitivity has been established and a feedback loop is formed that negatively impacts implant performance. We are currently investigating how the role metal-stimulated lymphocytes participate in the pathogenesis of aseptic osteolysis through the release of powerful cytokines such as IL-2, IFN-γ and RANKL (receptor-activated NF-KB ligand), which can directly increase bone resorption by osteoclasts and inhibit bone deposition by inhibiting osteoblast activity (Fig. 6.5) [124–127].

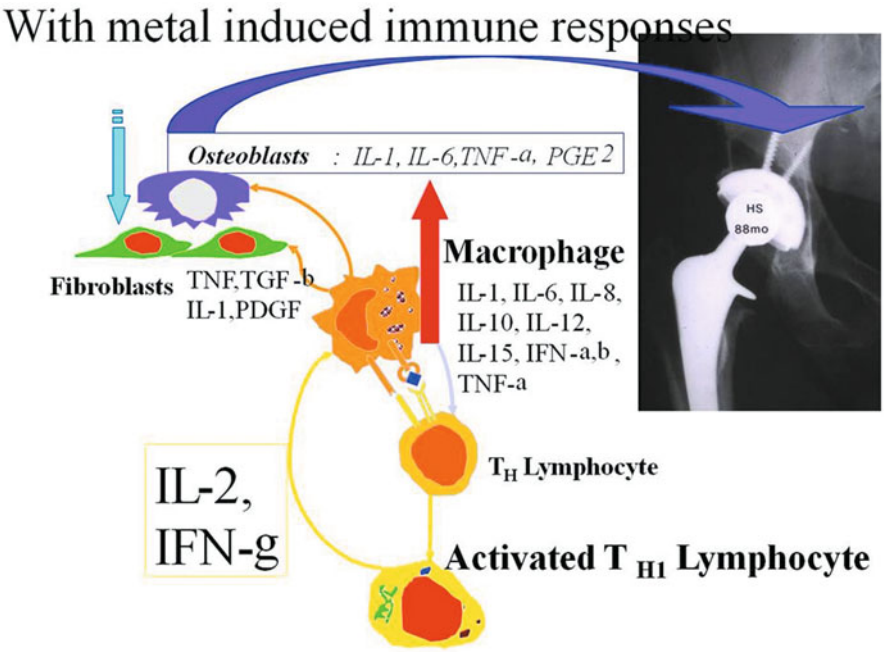

Fig. 6.5 Metal-induced immune responses can be due to both innate immune (e.g. macrophage) or adaptive (e.g. lymphocyte) immunity. Adaptive immune responses (i.e. hypersensitivity) can negatively effect bone homeostasis both directly and indirectly leading to osteolysis. (Courtesy of Orthopedic Analysis LLC)

Over the past 40 years implant-debris-induced inflammation has been characterized ad nauseam, where debris-induced localized inflammation is caused in large part by macrophages which up-regulate NFκβ and secrete inflammatory cytokines like IL-1β, TNFα, IL-6 and IL-8 [7]. Other anti-inflammatory cytokines such as IL-10 modulate the inflammatory process. Other factors involved with bone resorption include the enzymes responsible for catabolism of the organic component of bone. These include matrix metalloproteinases collagenase and stromelysin. Prostaglandins, in particular PGE_2, also are known to be important intercellular messengers in the osteolytic cascade produced by implant debris. More recently, several mediators known to be involved in stimulation or inhibition of osteoclast differentiation and maturation, such as RANKL (also referred to as osteoclast differentiation factor) and osteoprotegerin, respectively, have been suggested as key factors in the development and progression of bone loss (osteolytic lesions) produced from implant debris. Over the past 30 years we understand these mediators act to promote inflammation that decreases bone remodeling and is associated with the pathogenesis of osteolysis. However, we are only beginning to understand how implant debris could actually induce this immune system response at the cellular level.

Conclusions

When attempting to predict all of the effects of implant debris on the immune system, one of three possible outcomes could occur: (1) metal degradation products are immunogenic [39, 44, 128, 129], (2) metal degradation products are immunosuppressive [130–132] or (3) metal degradation products are immuno-neutral (i.e. non-bioreactive) [133, 134]. While all three possibilities have been shown to occur in reported case and group studies, the type of reaction and outcome that will occur in any one individual is mostly likely dependent on the individual (genetic regulation and immune status), the environment and the type of implant.

The key cell types in metal sensitivity are CD4+ lymphocytes, that traffic locally through the periprosthetic space. Upon metal exposure by APC the relevant lymphocytes proliferate and activate, which can potentially contribute to the cascade of inflammatory events leading to osteolysis and aseptic loosening. Pro-inflammatory cytokines are released such as IL-2, IFN-gamma and RANKL that can activate osteoclasts directly (increasing bone resorption) and inhibiting osteoblasts (decreasing bone production). Thus, as the number of patients receiving implants grow and the clinical specialties expected to evaluate this phenomena increases, metal sensitivity testing offers a relatively risk-free additional tool in the armamentarium of physicians/surgeons.

While positive results of sensitivity responses to metallic biomaterials which affect orthopedic implant performance in other than a few percent of patients (i.e. highly predisposed people) [135, 136] are growing, new evidence continues to demonstrate that concrete relationship and benefits of sensitivity testing may improve success rates of surgeons and satisfaction of patients [21, 30, 37].

Although the exact percentage of people that will develop metal sensitivity responses to their implant that results in early implant failure is unknown, it is clear some people experience excessive immune reactions to the metals released from implanted metallic materials [12, 81, 83, 84, 86, 94]. Metal sensitivity testing is currently the only form of testing in those individuals that are highly susceptible to excessive metal-induced immune responses (i.e. purportedly about 1 % of joint replacement recipients) [1] . Of the different forms of metal sensitivity testing, LTT may provide greater sensitivity relative to patch testing but larger clinical outcome studies that are needed to validate the sensitivity and specificity of patch testing or LTT (i.e. a clinically identifiable pathology), are still in progress [2, 22, 137]. Because there are different methods for conducting metal sensitivity testing and testing is a highly complex immune test, it is very important that any testing facility be both certified (by US law through the Clinical Laboratory Improvement Amendments (CLIA) agency, administered by the FDA), and is able to fully disclose all testing parameters to physicians, researchers and the general public. Physicians ordering this testing should be familiar with criteria such as (1) test conditions, including challenge agents (soluble and particulate), culture medium, time of incubation, etc, (2) method of proliferation detection, (3) whether autologous serum is used for culturing or if AB pooled serum is used to supplement human cell cultures, (4) if there is statistical

assessment or an acceptable level of redundancy, e.g. triplicate, duplicate, etc., (5) the pharmalogical profile of the patient at the time of testing and (6) if there is strict adherence to all patient privacy and Health Insurance Portability and Accountability Act regulations, required by law. Given that $< 1\,\%$ of the over 1 million people receiving total joint replacement implants in the USA annually are metal sensitivity tested pre-op or at revision, it is likely that implant-related metal sensitivity has been underreported [1, 3]. However, the slow and continuing improvements in sensitivity testing technology and availability will likely continue to provide accumulative clinical evidence into the utility of metal sensitivity testing along with more basic understanding into how and when metal sensitivity develops.

Recent results show that patients receiving implants who are diagnosed preoperatively by metal sensitivity testing have better outcomes than those for whom the results of sensitivity testing is not accommodated by altered surgical procedure [37]. More studies like this are needed to build a consensus and confirm the clinical utility of pre-op and/or post-op LTT, by demonstrating those tested have better outcomes when actions are taken to avoid the respective immunogenic metals compared to people tested who receive no evasive action. As these reports build scientific consensus, there is an increasing need to factor in the phenomenon of metal sensitivity and many surgeons now take this into account when planning which implant is optimal for each patient. Optimizing implant and material selection that is tailored to the immune reactivity profiles of each individual based on their genetic and environment history is paramount, as greater than 1 in 4 older Americans will eventually require a joint replacement implant [73, 138, 139] and early poor performance and revision surgery with a patient over the age of 75 can result in rates of mortality $> 10\,\%$ [140, 141]. Appropriate pre-operative testing that can extend implant performance in some cases is literally a matter of life and death and could decrease overall health costs.

Disclosures Dr Wooley is the Chief Scientific Officer of the National Center of Innovation for Biomaterials in Orthopaedic Research, inventor of the Arthrollergen^{TM} biomaterial sensitivity test, consultant to Stryker Orthopaedics, Inc, and consultant to the legal representatives of Depuy, Inc. Dr Wooley receives no financial benefit for these activities.

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Part III
Biology

Chapter 7
Wound Healing, Chronic Inflammation, and Immune Responses

Paul H. Wooley and Nadim J. Hallab

Introduction

In this review we will address the basic concepts of wound healing, chronic inflammation, and immune responses, and examine the influence of orthopedic metal alloys and their attendant ion species on these biological processes. Since the modern era of arthroplasty emerged, the ability to distinguish between biological responses to implanted materials and unrelated pathological events has proved difficult for the orthopedic scientific community. In an exchange between Charnley and McGee in 1957 at the Royal Society of Medicine [1] it was stated that "inflammatory complications may therefore still arise from the use of unsuitable metals, and if the surgeon is unaware of the danger he will naturally conclude that his wounds are becoming infected. . . . The answer to this question must come from the biological scientist, and then the complex problem of compatibility will no longer be studies in isolation." Unfortunately, biological scientists have yet to answer this complex problem after more than 50 years. It is important to recognize that the biological reactions to implanted materials cannot be simply reduced to concepts of "good" or "bad," but that biocompatibility must address performance in the application under consideration [2]. It is also important to recognize that three forms of metal may be encountered in the body as the result of an orthopedic procedure: solid metal components (such as fracture plates and femoral stems), particulate metal debris (the inevitable consequence of a metal bearing surface), and metallic ions (corrosion products that arise from the exposure of metals to plasma and cells). Biological responses to metals

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in particulate form share much in common with other stimuli of the inflammatory response (such as polyethylene wear debris), while metal ions have the capacity to exert direct effects on cells and are a requisition for the development of an immunological reaction to the hapten–carrier complex [3]. While wound healing, chronic inflammation, and the immune response share numerous common mediators and pathways, there are subtle variations between the processes that will influence the eventual biological resolution of any implanted material. Most of the pathways pertinent to these basic responses are under marked genetic regulation [4], meaning that the precise reaction of any given patient to a particular biomaterial is difficult, if not impossible, to predict. As recent research has revealed the relationship between responses to implant wear debris and osteolysis [5], it is perhaps remarkable from a biologist's perspective that arthroplasty has achieved the notable success that has been recorded in the modern era. However, it will take a further merger between biomechanics, biomedical engineering, and particle tribology to fully resolve the questions posed by the early and recent proponents of hip and knee prostheses. This chapter will review the primary pathways in cellular biology that regulate wound healing, inflammation, and immunity, with a particular focus upon common mediators that interact between the systems. We will further examine the current state of knowledge of the influence of metal in its various forms (solid state, wear debris, and metal ions) on these biological processes.

Wound Healing

Wound healing has been classically described at the level of skin repair, and may be divided into four phases (hemostasis, inflammation, repair, and remodeling). These basic principles are essentially common to all forms of tissue healing, although variations are observed in the joint connective tissues, with particular differences occurring during bone healing. *Hemostasis* is the immediate and shortest phase and occurs in the immediate seconds following the wounding event and has a duration lasting in the range of hours. Disruption of blood vessels and the release of plasma and cells into tissue trigger several events, with clot generation as the primary mechanism to prevent blood loss and inhibit the invasion of pathogens. Platelets adhere to exposed collagen fibers in damaged blood vessels, up-regulating platelet integrin αIIbβ3 to promote platelet aggregation [6]. Aggregated platelets release plasma coagulation factors to promote the formation of a fibrin clot. Both damaged tissues and implant surfaces can activate intracellular events that accelerate fibrin formation, and this phenomenon has been investigated to a reasonable degree with respect to dental and cardiovascular implants. In particular, titanium is recognized to increase platelet activation [7–9], and current research suggests that it is the surface topography of the material that exerts the greatest effect on platelet activation. The short-term release of growth factors, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor-β (TGFβ) may ultimately influence bone repair, since the osteogenic nature of platelet products is

well recognized [10, 11]. Overall the platelet-, fibrin-, and erythrocyte-aggregated clot serves as a temporary barrier to protect tissue integrity, but also forms a reservoir of cell signaling factors including fibronectin and vitronectin that orchestrate the next phases of healing [12]. *Inflammation* follows hemostatis rapidly, may last hours to days, and is initiated by chemoattractants released from platelets. Vasodilation and vascular permeability are locally increased, resulting in leucocyte recruitment at the site of tissue damage. Polymorphonuclear leucocytes (PMNs) are the first cells to accumulate at the wound site, and are present in high numbers within 24 hours. Expression of chemoattractants and adhesion moles on the endothelial cell surface facilitate the PMN migration to tissue, initially due to the interaction of P-selectin with its ligand PSGL-1 on the PMN cell surface [13]. Chemoattractants increase levels of β2 integrins on PMNs, which results in firm binding to endothelial cells via the intracellular adhesion molecule ICAM-1, and subsequent extravasation through the vessel wall into the wound site. The actions of PMNs are focused upon bacterial killing through phagocytosis and the production of nitric oxide, hydrogen peroxide, and proteolytic enzymes, but these cells can also remove tissue debris at this early phase. The wave of PMN accumulation is followed by the migration of peripheral blood monocytes to the wound site, mediated by the release of macrophage inflammatory protein (MIP-1B) and the chemokine (C-C motif) ligand 5 (CCL5 or RANTES) from local endothelial cells [14]. Monocytes differentiate into macrophages within the tissue, and represent an extended response to damage when compared with the short-lived PMN population. Macrophages are highly effective in both anti-bacterial activity and damaged tissue debridement, and are critical to the resolution of wound healing [15]. Macrophages release the pro-inflammatory cytokines IL-1β and TNFα, which are both autocrine and paracrine in nature. Due to the close relationship between macrophages and osteoclasts, these cytokines also up-regulate clastic activity and bone resorption, meaning that inflammation in close proximity to bone will affect bone remodeling [16]. While this is of little consequence during the acute inflammatory responses that typically characterize wound healing, it may have detrimental effects in the event that an inflammatory phase becomes chronic. Lymphocytes may also gain access to the wound site during blood vessel vasodilation and increased vascular permeability, and thus can respond to immunological stimuli at the site through interactions with phagocytic cells. However, in the absence of specific pre-exposure of the immune system to any pathogens that gain entry during the tissue damage, it is unclear whether lymphocytes play any direct role in the acute wound healing phase beyond immune surveillance. However, lymphocytes can express a broad range of cytokines such as IL-17 that both affect the inflammatory process and ultimately impact bone metabolism, thus lymphocyte activation status has the potential to influence the level, duration, and ultimate consequences of the inflammatory phase [17, 18]. Down-regulation of the inflammatory phase appears to be mediated at the level of the macrophage response, since transforming growth factor-β (TGFβ) and VEGF may ultimately be generated by the macrophage in a non-stimulatory environment [19]. These cytokines will attenuate the inflammatory response and promote the recruitment and proliferation of fibroblasts at the wound site. The *repair* phase of wound healing is characterized by fibroblast activities, and has a time

frame of days to weeks. Tissue repair requires scaffolding to provide both strength and the support for re-growth of the damaged tissues. Essential to tissue repair is the re-vascularization process to ensure sufficient nutritional support of active tissue growth and cellular proliferation. Extracellular matrix (ECM) is initially secreted to fill tissue voids, and the progression of fibrinogen and fibronectin to proteoglycans and collagens is orchestrated to achieve tissue repair. Variations in the repair process are notable between soft tissues and bone, and are influenced by the nature of the wound and the level of the attendance tissue loss. Wounds with no significant tissue displacement (such as surgical incisions) can be repaired by primary healing, as opposed to the secondary healing that requires void filling and marked ECM deposition [20]. Primary healing is orchestrated at the wound boundary, and skin repair is characterized by keratinocyte migration to achieve re-epithelialization of the skin surface. Keratinocytes attach to the fibrin clot and release matrix metalloproteases (MMPs) and tissue plasminogen activator (tPA) to modify the density of the clot matrix. Keratinocytes will bind to fibronectin and vitronectin via $\alpha 5\beta 1$ and $\alpha V\beta 6$ integrins [21, 22] and through a process of both migration and proliferation will provide complete coverage of the fibrin clot. Cell signaling via keratinocyte growth factor (KGF), epidermal growth factor (EGF), and TGFβ then promotes wound closure and the regeneration of the basement membrane [23]. In the event of a full-thickness skin wound and concomitant tissue loss, secondary healing is required to achieve the repair, and fibroblasts become the dominant cell for this process. These cells are stimulated by macrophage-released factors to migrate into the wound site and secrete fibronectin and collagens (primarily Type I and Type III) to form the initial ECM [20]. This scaffold is utilized by keratinocytes to achieve re-epithelialization, and the matrix evolves to contain hyaluronic acid which provides support for capillary budding and angiogenesis during the revascularization process [24]. VEGF and fibroblast growth factor-2 (FGF-2) serve to regulate these repair events [12].

The repair process in bone exhibits some notable changes from skin and soft tissues. Primary bone healing is highly dependent upon adequate stabilization of the bone surfaces to permit direct bone repair. The critical gap that can be healed by the primary process in bone is considered to be < 0.5 mm [25] and is mediated by osteoblast activities. Osteoblasts accumulate within the bone void under the effects of bone morphogenic proteins (BMPs) and secrete osteoid to fill the gap. This matrix, which contains primarily Type I collagen (and secondarily Type IV collagen) is then mineralized via the deposition of hydroxyapatite [26]. The residual osteoblasts then differentiate into bone resident osteocytes, but bone remodeling via the cyclic process of osteoclastic and osteoblastic activity is required to fully integrate the gap repair and restore the integral strength of the skeleton to pre-damage levels. In fracture repair with adequate reduction and stabilization, intramembranous ossification can occur across the fracture surfaces using direct lamellar bone production [27]. This process is driven by osteoclastic activity to expose bone pits that stimulate osteoblasts. Osteoclasts attach to bone via β3 integrins and form a ruffled border, and accumulate at the bone surface to form “cutting cones” [28]. Within these regions the bone surface is acidified, followed by the secretion of lysosomal enzymes to digest the organic components of bone. The ruffled border is maintained during bone

resorption through a balance between exocytotic and endocytotic processes within the osteoclast to achieve bone removal resulting in shallow erosive pits [29]. Capillary formation occurs within the cutting cones, and osteoblasts migrate to the region and commence osteoid deposition. Subsequent mineralization occurs to achieve union across the fracture line and complete the bone healing. However, in the event of inadequate fixation or excessive disruption of the bone surfaces, secondary bone repair or endochondral ossification involving fibrocartilage formation is employed to achieve union [27]. The periosteum serves to facilitate this process, which is characterized by fibroblast and undifferentiated mesenchymal cell accumulation within the local periosteal tissue within days of the injury. Chondrocytes (generated at the wound site from undifferentiated mesenchymal cells) and fibroblasts collaborate under the influence of PDGF, TGFβ, and FGF [30] to produce a fibrous tissue matrix termed soft callus. Soft callus is a fibrocartilagenous tissue that provides structural support for the fracture and stimulates neovascularization to promote the healing process, and is subsequently mineralized to hard callus after approximately 2 weeks. The mineralization process from fibrocartilage to bone involves removal of glycosaminoglycans from the collagen matrix by secretion of proteoglycanases [31], which is followed by mineralization of the randomly arranged collagen fiber network to result in woven bone. Bone remodeling via the cyclic process of osteoclastic and osteoblastic activity will then complete the formation of laminar bone and achieve full bone healing.

The aspects of *remodeling* vary between tissue types and the outcomes can show considerable variability. Primary wound healing in skin involves little remodeling due to minimal ECM disturbance, while secondary wound healing typically results in scar formation. Scar tissue arises from the failure to develop tissue reorganization consistent with the original (pre-wound) state, which leads to some level of fibrosis. Scarring in most tissues is characterized by fibroblast overproduction and deposition of Type I and III collagen, and this process is regulated by the Smad and STAT6 signaling pathways, characterized by TGFβ and IL-4, IL-13, respectively [32]. Resolution to scar tissue requires the differentiation of fibroblasts to the myofibroblast phenotype and an emphasis on the production of Type I collagen and alpha smooth muscle actin [23, 33]. Myofibroblasts exert contractile forces at the wound site that result in collagen fiber alignment parallel to the wound bed, resulting in striated scar tissue. Wound contraction eventually results in apoptosis of the myofibroblasts and increasingly acellular and avascular scar tissue with dense collagen bundles [34]. Remodeling time in skin is typically 3–6 months, and can achieve a maximum of 80 % of the pre-wound strength [35]. Bone is one of few tissues that can successfully remodel to essentially replicate the tissue status prior to injury. Primary and secondary healing in bone employs the same remodeling mechanisms, which are also the same processes that operate in bone tissue throughout life. The remodeling activities are driven through osteoclast adhesion to the bone proteins osteopontin, osteocalcin, and osteonectin [36] and the formation of cutting cones. The process is regulated through both soluble signals such as BMPs and also a mechanotransduction process designed to replace woven bone with lamellar bone aligned in response to stress forces. Numerous factors influence osteoclastic activity, although the dominant pathway that controls bone remodeling rate is the RANK/RANKL/OPG system [37].

The receptor activator of nuclear factor kappa-B (RANK), its ligand (RANKL), and the decoy receptor osteoprotegerin (OPG) form the central axis of what was once termed "bone coupling," and operate through the control of the rate of osteoclastogenesis. Central to the operation of this system is the nuclear factor of activated T cells c1 (NFATc1), which is activated by Ca^{2+} signaling associated with immunoreceptor tyrosine-based activation motif (ITAM)-harboring adapters [38]. Osteoclast activity is markedly influenced by the pro-inflammatory cytokines IL-1β and TNFα; the alpha(v)beta3 integrin-dependent signaling pathway, including c-Src, Pyk2, and p130Cas [39]; Cbl proteins [40]; a variety of calcitropic hormones (PTH, thyroid hormone, sex steroids) [41]; and modulators of cell trafficking such as sphingosine-1-phosphate (S1P) [42]. A complex set of signals balance osteoblast differentiation and activity in the remodeling process [43], with marked influences exerted by Wnt proteins that promote differentiation of osteoblasts [44] and influence the production of sclerostin [45], the regulators of the RunX2 and Osterix gene systems [46], and prostaglandin production [47]. In the healthy individual, there is a remarkable capacity to repair bone, but it should be noted that the presence of connective tissues diseases, particularly those with an underlying autoimmune pathology, have the capacity to markedly diminish the outcome of the wound-healing process.

Chronic Inflammation

The acute inflammatory process has been described as a protective part of wound healing, and we will now examine the processes that lead to chronic inflammation and its attendant pathophysiology. Since the mediators of acute inflammation are relatively short lived, chronic inflammation only arises due to persistence of the stimulus and the resultant effects upon the macrophage population. A combination of the dysregulation of apoptotic activity that reduces macrophages at the site of inflammation and the maintenance of a high macrophage activity status appears to be critical to the prolongation of macrophage survival and thus the progression from acute to chronic inflammation [48]. Paradoxically, phagocytosis of apoptotic cells or apoptotic bodies inhibits macrophage apoptosis via activation of protein kinase B (PKB), and inhibition of the signal-regulated kinases (ERK)1 and (ERK)2 [49]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (CSF-1) appear to be the key mediators in the maintenance of macrophage activity at the site of inflammation [50, 51], and recent studies have demonstrated that Toll-Like receptors (TLRs) and NOD-like receptors (NLRs) trigger intracellular signaling pathways critical to the inflammatory response [52]. TLRs recognize microbial products and endogenous molecules released during cell damage and necrosis [53] and exert a marked influence upon fibrosis [54] and the chronicity of the inflammatory response [55, 56]. Classical studies have demonstrated that bacterial species that avoid elimination by the phagocytic process are typical candidates that provoke the progression from acute to chronic inflammation [57]. It should not therefore be surprising that orthopedic

wear debris, which mimics the size range of typical pathogens and resists phagocytic clearance due to the absence of appropriate enzymes in mammalian species, can also provoke chronic inflammatory responses [58]. Two types of chronic inflammation are usually encountered during the evaluation of aseptic biomaterial responses in connective tissues: granulomatous inflammation (characterized by an organized collection of macrophages) and fibrinous inflammation (characterized by a fibrous exudate and scar formation). Granulomatous inflammation can be considered as a concerted effort to "wall off" the inflammatory stimulus behind a fibrous capsule, which can ultimately become calcified to further alleviate any further exposure of the foreign material. Pseudosynovial tissues recovered during revision arthroplasty reveal a self-perpetuating fibro-inflammatory zone adjacent to the implant, where macrophage exhaustion, reactive oxygen intermediates, and pro-inflammatory cytokines contribute to chronic inflammatory changes [59]. Fibrinous inflammation in combination with granulomatous inflammation can be considered as the typical picture in the peri-prosthetic capsule, since isolated fibrinous inflammation only appears during perivascular inflammation [60, 61]. Interestingly, fibrinous inflammation has been described as the dominant pathology in the synovial response to articular wear products from cartilage and bone [62]. Overall, the pseudosynovial capsule that develops following joint arthroplasty can be expected to be the major repository of wear debris that arises from the movement of the prosthesis-bearing surface, and will exhibit some level of chronic inflammatory response due to the biological response to wear debris [5]. Most reactions to metal debris are similar to the responses to other bearing materials. The term "metallosis" originated in the 1950's during the investigation of metal effects on tissues, particularly the products of corrosion [63–65] from a variety of orthopedic devices. Both metal debris and corrosion products are usually characterized by discoloration of tissue to tan, grey, or black, although this color change is not synonymous with necrotic changes in tissue. Metal levels considered toxic have not been defined for patients with orthopedic devices [66, 67] and systemic effects of metal ions appear to be uncommon [68]. The major initial concern with the appearance of metallosis was the potential for misdiagnosis as major infection [69]. Metallosis is now widely applied to describe the accumulation of metal debris within the capsular tissue, but should not be considered as specific for metal-on-metal (MOM) bearings [70, 71]. The term "adverse reaction to metal debris" or ARMD is a fairly all-encompassing term that has been used to describe the predominantly chronic inflammatory changes in capsules associated with MOM bearings, while cross-referencing the lymphocytic involvement that is observed in the tissues [72]. This inflammatory reaction varies widely between patients, and even within individual tissues the inflammation can show regional variations in intensity, although histiocytes containing metal debris is an essentially universal finding. A recent study [73] indicating a poor association between ARMD and blood metal ion levels suggests that the inflammatory reaction to wear debris remains the dominant aspect of the pseudosynovial response associated with MOM implants. The descriptor "pseudotumor" has also become synonymous with MOM implants, although an inflammatory mass composed of fibrous and/or granulation tissue infiltrated by inflammatory cells is a fairly common response to an accumulation of any wear debris

or other material stimuli [74–79]. Matthies et al. [80] suggest that pseudotumors are not associated with increased wear or metal ion levels, and indicated that patient susceptibility is likely to be more important in the development of this pathological feature. Hart et al. [81] reported that the prevalence of pseudotumors was similar regardless of whether hips were functioning well or poorly, which again supports the concept of a patient-based response in pseudotumor formation. The finding of lymphocytic accumulation within the inflammatory capsular tissue does appear to be fairly common for retrievals of MOM implants [82], but this phenomenon is also not specific for this type of bearing material [83, 84]. Therefore the significance of these aspects of the capsule pathology needs to be placed in the context of the immunological response.

Immune Responses

The mammalian immune system is a highly evolved network designed to provide specific responses to environmental insults and pathogens. Immunological responses are typically triggered through threshold events—if a minor bacterial invasion is rapidly cleared through the phagocytic response, there is no requirement for lymphocyte involvement. However, persistence of antigen or repeated exposure to foreign entities will provoke the specific targeted response. The macrophage is the key cell in the discrimination between "self" and "non-self" within the body and the processing of foreign material [85]. Antigens (foreign cells or components) are reduced to epitopes (the precise targets of an immune response) in the phagosome environment and are then presented in context of the individual's tissue antigen (Class II MHC antigens) to CD4+ T helper cells. This process is further regulated by T cell co-stimulatory molecules (the B7 complex of CD80 and CD86, and ICAM-1) expressed on the macrophage population and T cell second signal molecule CD28. The T cells will subsequently recruit specific B cells to differentiate into antibody (IgM) secreting plasma cells or (dependent upon the nature of the antigen) will recruit other T cells (effector cells) that eliminate target cells expressing the antigen [86]. The primary response is rapid (7–10 days) and there are no adverse effects in a patient during this initial phase of immunity. At the conclusion of the primary response, T cells and B cells differentiate into "memory" cells that retain the specificity for this antigen, and enable a rapid response on repeated contact with the same antigen. Subsequent or chronic exposure to an antigen results in an elevated immune response designed to rapidly eliminate a pathogen through heightened activity and increased specificity against the antigen. On occasions, the secondary immune response can lead to adverse patient reactions [87, 88]. The term *hypersensitivity* denotes an excessive immune response that results in some degree of tissue damage. Hypersensitivity reactions have been historically classified as one of four types: Type I = immediate hypersensitivity mediated by IgE antibody responses; Type II = antibody-mediated cell cytotoxicity; Type III = immune complex-mediated tissue damage; and Type IV = delayed-type hypersensitivity or T cell-mediated reactions [89]. Each of these

groups can be sub-categorized to some extent. However, the majority of allergic responses can usually be defined as either Type I or Type IV hypersensitivity, and we will examine the response to metal stimuli in context of these two types. It is important to remember that patients only develop "allergic" responses following secondary or chronic exposure to an antigen. Immediate (Type I) hypersensitivity arises due to the differentiation of B cells into plasma cells that secrete IgE. The induction of IgE appears to require the binding of allergen by B cells (via surface immunoglobulin), internal antigen processing by the B cell, and the production of both IL-4 and IL-13. The switch from IgM to IgE occurs due to sequential deletional events at the B cell gene level, and may transpire following a switch from IgM to IgG rather than a direct switch. IgE antibody bound to antigen engages mast cells via the epsilon receptor, and causes degranulation with the release of histamine, giving rise to symptoms typical of hay fever [90]. Type I hypersensitivity appears to have evolved as a weapon against parasite antigens, since local histamine release appears to perturb the attachment of skin parasites such as ticks, and reduce colonization by helminths (worms) [91]. Chronic exposure to antigen can also result in delayed (Type IV) hypersensitivity, which is T cell mediated, and (as the name implies) produces tissue reactions after a minimum of 12 hours and usually peaks by 72 hours. The most common clinical problem that arises from Type IV hypersensitivity is contact dermatitis, which usually presents as an epidermal phenomenon [92, 93]. Antigens that provoke contact sensitivity are frequently chemical in nature such as nickel and the components of poison ivy and poison oak. These low-molecular-weight chemical entities are not freestanding antigens, but are classified as haptens. Haptens are entities that can bind to (native) proteins such as albumin, and modify the conformational structure so that the hapten–carrier conjugate is recognized as foreign by the immune system. Langerhans' cells predominate in the presentation of antigens that provoke contact sensitivity, both within the skin and following the migration of these sensitized dendritic cells to the lymph node [94]. T cells that recognize haptens migrate to sites that contain the sensitizing antigen (usually skin), where they mediate inflammatory reactions that result in tissue damage. These cytotoxic T cells are frequently CD4+, although CD8+ T cells are also seen at the reaction sites. The local skin reaction that characterizes contact dermatitis frequently results in expression of Class II MHC antigens on keratinocytes, which may be indicative of abnormal antigen presentation during the response [95].

Solid metal alloy components of orthopedic prostheses are clearly beyond the size range of entities expected to generate classic immune responses. It requires four factors to occur in order to develop metal hypersensitivity: (1) the release of metallic ions from the metal through to the corrosive action of plasma, sweat, or the phagosomal environment of the macrophage, (2) the coupling of the ions to an endogenous protein or cell to form a hapten–carrier complex, (3) the accumulation of the hapten–carrier complex to a threshold level that can trigger a primary immune response, and (4) continued chronic exposure to the hapten–carrier complex. Metal ions may also act directly upon cells of the immune system, and mediate abnormal sensitivity due to toxic or stimulatory effects [96] and up-regulation of T cell co-stimulatory molecules [97]. The capacity of several orthopedic metals to elicit contact

hypersensitivity responses is well recognized, although classic sensitivity appears to be somewhat uncommon for most orthopedic devices, and nickel appears to be the most common sensitizing allergen. Studies suggest that nickel reactivity affects 5–15 % of women and 1–2 % of men in the North American population [98, 99]. There appears to be a mild genetic regulation to nickel allergy, with a relative risk of around 2.83 in first-degree relatives of sensitive patients [100]. The marked sex variation between nickel sensitivity is believed to be associated with jewelry [101], particularly the practice of body piercing [102]. As this phenomenon is becoming more common in men, it will be interesting to observe whether the incidence of metal sensitivity in males rises in the future. Allergic contact dermatitis has also been reported from prolonged contact with the orthopedic prostheses worn by amputees [103]. In a study of eight lower-limb amputees with dermatitis of the lower limb, one patient was found to be nickel sensitive, while three others displayed responses to resin components.

Early studies do suggest that metal sensitivity (defined by skin testing) appears to be elevated in arthroplasty patients with well functioning implants, and may be further elevated in candidates for revision surgery. Elves et al. [104] examined 50 patients and reported a 38 % positive skin patch reaction to one or more of an allergen library consisting of chromium, cobalt, nickel, molybdenum, vanadium, and titanium. The incidence in revision surgery patients was elevated to 65 %, while only 15 % of patients with stable arthroplasties were contact sensitive, and the positive reactions were limited to nickel and cobalt. Evans et al. [105] also reported an incidence of metal sensitivity of 65 % in patients with loose prostheses, with no sensitivity in 24 patients with intact joint implants. The specificity of the response to the individual metals is important, since broadened metal sensitivity does not usually arise due to cross-reactivity [106]. It should be noted that it is uncertain whether aseptic loosening causes metal sensitization, or is the result of elevated ion exposure due to particles shed from a failing metal component. Thus, it is controversial as to whether metal hypersensitivity can contribute to the pathology of aseptic loosening [107–110]. Nevertheless, the prevalence of metal sensitivity in patients with failed implants is six times higher than the population at large and three times higher than the implanted orthopedic population [111]. However, experimental findings in guinea pigs sensitized to nickel, cobalt, or chromium have suggested that an ongoing allergic response was without effect upon the fixation of bone screws [112, 113]. A relevant study was conducted by Carlsson and Moller [114] who analyzed 22 patients with known metal allergies having orthopedic prostheses. Interestingly, on retesting for metal allergy, four of the patients proved patch test negative and were eliminated from study. After a mean of 6 years follow-up, it was found that no orthopedic or dermatological complications were reported, although three cases of eczema and two prosthesis failures were documented. The implants were a combination of nine fixed devices and nine hip or knee arthroplasties.

The most common presentation of complications in metal-sensitive patients appears to be a contact dermatitis-like condition [115]. Brjurholm et al. [116] found two nickel reactive patients in 14 patients with local or widespread eczematous lesions following nail-fixed fractures, compared with no responders in a matched set

of 13 fracture controls. A similar frequency was observed by Kubba et al. [117] in a prospective study of cutaneous complications of orthopedic implants at the Cleveland Clinic. Two clinical patterns were observed: A transient "exanthematic" dermatitis was seen in six patients; in two of them, it recurred after each surgical implant procedure, and the outcome was described as an urticarial eruption in one of these patients. Histological findings were non-specific, with a moderate perivascular inflammatory infiltrate being the main biopsy finding. A persistent reaction was seen in 13 patients, and metal sensitivity determined by patch testing was found in three patients. Two patients with static implants (intramedullary nail; stainless steel screws) reacted to nickel and chromium, and nickel and resin, respectively, while one patient with a hip prosthesis reacted to nickel and cobalt. The authors commented that a causal relationship was probable, and in the 19 patients with skin reactions, loosening of the implant was reported in three cases. The authors suggested that the incidence of cutaneous reactions following orthopedic implantation appears to be low, but may be under-diagnosed. The precise relationship of metal allergy to orthopedic complications remains unclear, and hypersensitive patients appear to be a subset of the orthopedic dermatitis population. In other clinical settings, metal sensitivity appears to be more directly related to complications. Lhotka et al. [118] examined reactions to metal skin clips in wound healing in a large ($n = 184$) patient base. As expected, nickel responses were most common when compared with the other metallic ions in skin clips. Males exhibited an 18 % positive response, while a 23 % response rate was observed in females. Clinical reactions were seen in all of the nickel responders. A total of 47 patients developed rash, eczema, blisters, or edema in the wound closure, and most of them experienced delayed wound healing. Two patients experienced a generalized allergic response. The authors concluded that delayed wound healing was strongly associated with metal allergy. This opinion is supported by Oakley [119], who described four patients with nickel allergy who developed generalized dermatitis following wound closure with stainless steel clips. Ross et al. [120] reported a case of severe allergy to nickel and cobalt following implantation with a stainless steel aneurysm clip. Symptoms appeared after 1 month, and it was subsequently discovered that the patient had a history of jewelry allergy. Following explantation, the patient's symptoms began to subside after 2 days, and were completely resolved by 6 months. Surgical wire may also represent a source of reactive ions. Fine et al. [121] have suggested that the common problem of persistent sternal pain following median sternotomy could be related to metal allergy. He described a case of pain in a highly nickel-sensitive patient that resolved on removal of the sternal wires. However, the associated rash was attributed to Zostrix rather than hypersensitivity to nickel. Gordon [122] described a similar case, although the patient, who was nickel patch test positive, did not react to the wire directly on skin testing. Nevertheless, explantation was performed and the patient responded immediately. Wires do not have to be implanted internally, since nickel–titanium orthodontic arch wires can apparently also sensitize individuals [123, 124].

There is a reasonable association between positive skin tests and lymphocyte proliferative responses to nickel salts [125], and phenotypical analysis of the nickel-specific T cell lines indicated that the response is predominantly mediated by CD8+

T lymphocytes bearing the alpha beta T cell receptor [126]. This suggests that metal sensitivity is mediated via classical immune response mechanisms, and indicates that metal haptens are recognized by standard antigen processing systems using normal transporter-associated antigen-processing (TAP) gene mechanisms, although an increased prevalence of the TAP2B allele has been identified in nickel-allergic patients [127]. Reports confirm that the regulation of the nickel-specific T cell response is mediated by CD4+ T lymphocytes [128], and that Class II MHC antigens restrict the response [129]. Other reports [130–132] indicate that T cell receptor subsets may be biased in CD4+ T cells from hypersensitive individuals responding to nickel, with over-representation of the Vβ17, Vβ13, Vβ20, Vβ2, or Vβ14 phenotypes. These observations suggest that classic immunogenetic regulation applies to nickel hypersensitivity, and, therefore, patients at risk could possibly be identified via human leukocyte antigen (HLA) phenotyping and T cell subset analysis. Further, regulatory nickel-specific CD4+ T cells with the potential to down-regulate nickel reactivity via IL-10 secretion have been identified, indicating potential immunotherapeutic approaches to the control of metal contact hypersensitivity.

Peripheral blood cells from patients with aseptic loosening do exhibit elevated in vitro responses to metals. Granchi et al. [133] reported that a chromium extract significantly increased the expression of the activated T cell (CD3/CD69) phenotype. A chromium-induced "activation index" was higher in patients with loosening of hip prosthesis than in healthy donors and pre-operative patients, while lymphocyte activation due to chromium stimulation was higher in implant recipients (irrespective of the prosthesis status) when compared with healthy donors. In vitro studies have also suggested that metal ions released from implants may have direct effects on immune function and lymphocyte surface antigens. Fe^{3+}, Ni^{2+}, and Co^{2+} have been shown to cause inhibition of the T cell antigen CD2, which may interfere with T cell activation since both CD2 and CD3 are involved in the antigen recognition process [134]. Akbar et al. [135] have demonstrated that exposure to high concentrations of metal ions can initiate apoptosis that results in decreased lymphocyte proliferation, and 10 μM cobalt (Co^{2+}) in culture led to significant decreases in cell proliferation and cytokine release. A T cell line has also been shown to undergo reduced cell viability and proliferation when exposed to nickel and vanadium metal ions in a dose-dependent manner. The reduced function appeared to be associated with the induction of apoptosis [136]. Therefore, direct metal ion effect on immune cells may be complex and dependent upon concentration, cell type, and genetic regulation. The development of responses to metal ions has been detected in 26 % of patients post-operatively using cell migration assays [137], and we have used cell proliferation techniques to examine cellular responses to orthopedic alloys [138, 139]. Our finding indicated that the response to Co–Cr (but not Ti-6-4) was significantly higher in revision surgery patients compared with a pre-operative primary surgery group ($p < 0.05$). Further analysis revealed that elevated responses to Co–Cr were observed in patients undergoing revision surgery due to painful prostheses or aseptic loosening ($p < 0.05$ and $p < 0.01$, respectively), while responses to Co–Cr in patients undergoing revision surgery due to mechanical failure or infection were similar to the responses in the pre-operative primary surgery group.

In addition to cellular reactivity to metals, there is evidence that hapten–carrier complexes containing metals may lead to antibody formation. Yang and Merritt [140] conjugated Cr, Co, and Ni ions to albumin bound on an enzyme-linked immunosorbent assay (ELISA) plate, and found that IgE (from the sera from arthroplasty patients) binds to these metal–albumin complexes. Remarkably, all patients examined developed IgE antibodies (the hallmark of Type I immediate hypersensitivity) against at least one metal, and a high incidence of IgM, IgG and IgA antibodies were also recorded. The potential for hapten–carrier stimulation using these metal ions was confirmed by the injection of rabbit albumin–glutathione–metal complexes into mice, which resulted in strong serum antibody reactions [141]. However, the presence of an antibody response to metal–protein complexes has not been associated with a poor surgical outcome. Reactivity to metals may be enhanced by the inflammatory reaction to peri-prosthetic wear debris. Elevated levels of IL-1β and GM-CSF have been seen in cells stimulated in vitro with prosthetic metal particulate material, to a level comparable to mitogen activation [142]. Cobalt–chromium particles have been shown to induce histiocytic responses and the production of IL-1β and prostaglandin E2 in a canine model of aseptic loosening [143].

There is agreement among several laboratories that differences exist in cellular reactivity induced by titanium–aluminum–vanadium alloy and by cobalt–chromium alloy. Haynes et al. [144] noted that Ti-6-4 increased the release of PGE2, IL-1β, TNFα, and IL-6, while Co–Cr was associated with a decreased release of PGE-2 and IL-6. Wang et al. [145] found that Ti, Cr, and Co enhanced the release of IL-1β from monocytes, Ti and Cr enhanced the release of TNFα, and Ti alone enhanced the release of IL-6. It also appears that the morphology of the cellular response in the peri-prosthetic region of the loosened implant varies between Co–Cr and Ti-6-4 [146]. Given the specificity of the immune system, this suggests that the selection of a different alloy in a pre-sensitized patient may be a useful strategy to circumvent any potential adverse effects that might arise due to immune reactivity to biomaterials.

An immune response to orthopedic biomaterials that results in an adverse outcome of joint arthroplasty is a relatively infrequent occurrence. While this is fortunate for the practice of orthopedic surgery, the low prevalence has led to poor diagnostic procedures and prophylactic activity. Surgeons should be familiar with the warning of known adverse reactions to materials that is included in the package insert, and obtain a pre-operative history that could alert them to potential problems in all patients. The early opinion by Rooker and Wilkinson [110] that "there is little evidence of a direct causal relationship between metal sensitivity and subsequent loosening" should not be interpreted to read that an allergic response to orthopedic is a trivial consideration for the orthopedic surgeon. It has been long purported that metal sensitivity responses contribute to the failure of some implants [107]. A relationship between reactivity to chromium, cobalt, or nickel and complications due to dental devices has been well established [147], with a convincing subsidence of clinical reactions associated with the removal of the suspected biomaterial. These findings stand as a cautionary note for the use of all implanted devices. The minimum consideration in the orthopedic patient is to enquire concerning allergic reactions to jewelry, dental amalgams, and methacrylate-based glues. Since jewelry reactions

are not uncommon, the self-identified positive patient should be further assessed to evaluate whether there is a pre-existing response to orthopedic alloys. First, many self-identified jewelry responders do not prove positive to classic skin tests with either metals or salts, and do not exhibit unusual in vitro cellular responses to biomaterials [148]. This information may provide a degree of re-assurance to both the patient and the surgeon, and can be determined by any competent allergist or immunologist. However, it should be noted that skin sensitivity to metals can be a subtle response and the classic "wheal and flare" skin reaction is rarely seen. Some patients do show a strong contact reaction, with a marked pruritic, erythematous rash extending beyond the test area. This type of response is hard to ignore, and certainly raises several flags for the selection of materials. Our laboratory and others [125] have found a good correlation between positive skin tests and hyper-proliferation of cells cultured in the presence of a specific biomaterial. However, this association is by no means absolute, and discordance between the tests can occur. Most investigators agree that it is more common to see a negative skin test and a positive in vitro reaction than vice versa [149]. As in all immunological tests, the current pharmacological profile of the patient should be evaluated to note any medications that can disrupt cellular responses to antigenic stimulation. Although the value of the hypersensitivity test in predicting an adverse outcome is not clear cut [150], orthopedic immunologists generally feel that this information should be part of the global surgical decision making. The most common situation where immune reactivity becomes an issue is retrospective to the surgical procedure. The usual presentation to the orthopedic immunologist is a patient with a poor post-operative course, a painful prosthesis, and chronic drainage from the implantation site. Invariably these patients have been extensively worked up for an infectious etiology, with a string of negative findings. The fluid draining from the site is frequently rich in lymphocytes, and polymorphonuclear leucocytes (PMNs) are less well represented that would be expected in infection. A review of the immediate post-operative course can prove useful, particularly if the patient exhibited any inflammatory reaction to surgical staples [118]. Skin clips may contain chromium, nickel, molybdenum, cobalt, and titanium in concentrations high enough to cause contact reactions, which may delay wound healing. Should a reaction to staples be noted, the surgeon should have concerns for the prosthesis, since this reaction is indicative of pre-existing metal sensitivity. The patient may experience febrile episodes, with or without local inflammation at the implant site, since fever is consistent with a hypersensitivity response. Another useful criterion is the appearance of skin rashes, which are not necessarily close to the wound site. Rashes on the arms, legs, and trunk can occur when the metal hapten–carrier complex becomes trapped in the capillaries of the skin, or metal ions become directly coupled to keratinocytes [151] and dendritic cells [152, 153] or concentrated within skin cells [154]. T cells then migrate to these sites and cause inflammatory tissue damage, resulting in the appearance of a rash. However, the problematic patient may have a normal post-operative recovery and only present with a painful prosthesis with poor fixation after a considerable time period (6 months–2 years). In this instance, it is possible that an immune response has developed to the prosthesis itself. Several processes must occur for this to happen. First, for metal allergy to develop there must be sufficient

ion release from the metal components to generate a hapten–carrier complex. Then the hapten–carrier complex must accumulate to a threshold level in order to trigger the primary immune response. The threshold level for a response in humans has not been accurately determined and is predicted to vary widely among different individuals. Based mainly on animal studies, antigen threshold levels are usually considered to be around 1 μg, with the caveat that typical (protein) antigens have been used for this determination [155]. However, this figure is not grossly different for the nickel threshold, proposed by Gawkrodger [109], of 0.5 $\mu g/cm^2$/week for exposure. Since the rate of metallic ion dissociation from 316L stainless steel has been determined to be 0.03 $\mu g/cm^2$/week [156, 157], this suggests that at least 8 weeks would be required to provide sufficient ion release from a femoral component to stimulate the primary immune response in a "worse case" scenario. This hypothesis is consistent with the observation by Cramers [158] that contact sensitivity took 3–3.5 months to develop in patients implanted with plates and screws made of 316L stainless steel. Ion leakage may be accelerated by a number of factors, such as crevice corrosion, so the implant design may influence the potential for a device to stimulate an immunological response.

Implant wear may be particularly important for typical orthopedic alloys, since the production of small particles increases the surface area for ion generation and promotes the exposure to phagocytic cells and the acidic environment of the phagosome [159], leading to a proinflammatory response through the inflammasome pathway [160]. Agins et al. [161] conducted retrieval analysis on eight peri-prosthetic (dry) tissues from titanium alloy implants using atomic absorption spectrophotometry, and reported a mean accumulation of 1047 μg/gm titanium, 115 μg/gm aluminum, and 67 μg/gm vanadium. The accumulation increased with time after implantation, but all values were significantly elevated over normal tissue levels as early as 11 months post surgery. These metal levels may be high enough to have deleterious effects upon cells in the local area, although the development of immune responses was not documented in these patients. Membranes from the titanium-alloy implants tend to contain more metal debris than those from the cobalt–chromium-alloy implants, although levels of inflammatory cytokines and tissue metalloproteinases were not significantly different between the two orthopedic alloys [162]. Since metal-on-metal (MOM) implants are currently under scrutiny in orthopedic surgery, it would be valuable to follow these patients for the development of immune sensitivity. Reports concerning early MOM devices suggested that up to half of the surgical failures might be attributed to metal allergy [163]. More recent findings indicate that Co–Cr wear particles from MOM bearings may be considerably smaller than the typical particle size range reported for ultra-high molecular weight polyethylene (UHMWPE) particles[164]. It was suggested that metal particles may corrode and disseminate from local tissue sites to a higher degree than UHMWPE particles, and there is evidence to support this concept from atomic absorption spectrophotometry conducted upon lymphoreticular tissues [165]. This may influence immunological activity, indicated by a case report of lymphadenopathy [166], and an extensive examination of debris in para-aortic lymph nodes and spleens [167]. It should be considered that this resolution of metal from the peri-prosthetic area may be accompanied by a higher

systemic exposure to metal ions, which may result in an elevated potential to elicit metal sensitivity in genetically susceptible individuals.

Recently, concern has been generated regarding pseudotumor-like periprosthetic tissue reactions around MOM hip replacements that have led to revision surgery. The cause of these reactions remains controversial but excessive wear due to cup malalignment and metal hypersensitivity have been proposed in the etiology [168, 169]. Campbell et al. [170] have examined the synovial lining integrity, inflammatory cell infiltrates, tissue organization, necrosis, and metal wear particles of pseudotumors from MOM hips revised for suspected high wear related and suspected metal hypersensitivity causes. The term "aseptic lymphocytic vasculitis-associated lesions (ALVAL)" has been coined to describe the pathology that is observed in these cases [82, 171, 172]. The use of the term "vasculitis" may not be strictly accurate, since the pathology appears to involve the blood vessel thickening and high endothelial venule (HEV) development that is associated with lymphocyte tissue trafficking and perivascular lymphocyte accumulation, rather than a true inflammation of the blood vessels. However, the perivascular lymphocytic response may in turn cause vascular damage [72], although these changes may be related to the synovial effects of musculoskeletal disease [173]. Nevertheless, the increased interest on the lymphocyte participation in the pathology has focused interest on possible immune involvement in failed MOM devices, although no immune specificity has been associated with cellular infiltrate to date. ALVAL scoring has attempted to classify the degree of biological reactions that occur in the various regions of the pseudosynovial capsule, although it should be noted that most of the pathological features are also present in tissues retrieved from metal-on-polyethylene revision arthroplasties [5]. Campbell et al. reported that tissues from patients revised for suspected high wear had a lower ALVAL score, fewer lymphocytes, but more macrophages and metal particles than those tissues from hips revised for pain and suspected metal hypersensitivity. The highest ALVAL scores occurred in patients who were revised for pain and suspected metal hypersensitivity, and component wear was lower in that group [170]. Their conclusion was that pseudotumor-like reactions can be caused by high wear, but may also occur around implants with low wear, possibly because of a metal hypersensitivity reaction. This immunopathology was supported by the findings of Willert and others [174, 175, 176]. However, it should be noted that the immunological reaction may be more complex than standard Type IV hypersensitivity, and may extend to B lymphocyte sensitivity [177]. Delaunay et al. [178] noted that although ALVAL or a delayed Type IV hypersensitivity reaction may be the source of arthroplasty failure, the association is unpredictable using contact tests and is apparently rare (0.3 %). He also noted that no scientific or epidemiologic data support a risk of carcinogenesis or teratogenesis related to the use of a MOM bearing couple. Pseudotumors were usually associated with resurfacing procedures, particularly in women under 40 years of age [179], and increased with acetabular malposition and the use of cast-molded Cr–Co alloys. The formation of wear debris exceeding the biological tolerance is possible with implant malposition, subluxation, and edge loading of the femoral head. Delaunay opined that MOM bearing couples are contra-indicated in cases of metal allergies or end-stage renal dysfunction, and small-size resurfacing should

cautiously be used. Rajpura [180] described a revision series for 13 ALVAL patients and noted groin pain present in all patients usually accompanied by bursal swelling and mechanical symptoms, although pain was not always indicative of the diagnosis [181]. The mean time to presentation was 21 months post-operative. Radiographic abnormalities noted included cup loosening and neck thinning, with a mean cup inclination of 52°. Surgical findings included bursal swellings and creamy brown fluid, but osteolysis was rarely seen. Twelve revisions were achieved with primary implants and all patients had immediate symptomatic improvement. The diagnosis of ALVAL was confirmed histologically, and it was concluded that symptoms tend to resolve reliably following conversion to an alternative bearing surface.

Conclusions

While adverse reactions to metals appear to be an infrequent event in patients, we currently have only a limited capacity to diagnose the contribution of these reactions to orthopedic complications, and an even weaker ability to identify patients at risk prior to the selection of appropriate prosthetic components. Part of the problem is the complexity of joint replacements. While it is relatively easy to investigate immunotoxicological reactions to individual components in virgin form, it is a completely different problem to interpret the inflammatory and immune interactions in tissue chronically exposed to particulate debris from a metal implant. Some publications do support the existence of causal relationships between metal allergy and implant failure, but this concept is controversial since the co-incidence of these conditions without significant pathology suggests that this is a rare occurrence and difficult to substantiate under ideal circumstances. The issue relating to adverse tissue responses associated with resurfacing procedures is, therefore, not new, but may result from a combination of poor cup positioning and elevated biologic responses including metal hypersensitivity.

In the previous chapter we examined how the basic molecular and regulatory aspects of wound healing, chronic inflammation, and immune responses impact our capability to diagnose metal sensitivity in a clinical setting and interpret the effects on the outcome of orthopedic procedures. Many of the basic science observations described here result from carefully controlled laboratory setting using cell lines, animal models, and molecular tools. It should, therefore, be noted that generalization from these studies and even published clinical investigations to specific patient situations can be difficult. Charnley and McGee [1] did not foresee the complexity and interactions of the biological systems involved in metal hypersensivity, and the definite answers into the development and regulation of biological responses to metals remain to be elucidated.

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Chapter 8
Benign Responses to Orthopaedic Implants: Really?

H. John Cooper and Joshua J. Jacobs

Introduction

Wear particles generated by modern metal-on-metal (MoM) bearings are nanometer in size (mean 30–57 nm) [21, 34, 37], approximately an order of magnitude smaller than the size of polyethylene particles produced by metal-on-polyethylene (MoP) bearing surfaces. Although linear wear rates reported in MoM bearings are extremely low (5–45 μm during the first 2 years, and 2–15 μm thereafter) [17, 110, 118], the number of nanometer-sized particles generated can be up to 500 times greater than in MoP bearings [118].

The nanometer size and abundant nature of these metal particles means they may be widely disseminated into the local periprosthetic tissues and throughout the body. Furthermore, the biologic activity is a function of the particle size and relative surface area [43, 71]. Dissolution of metal particles also results in measurable increases in metal ion levels in serum, erythrocytes, and urine. De Smet et al. demonstrated that serum metal ion concentrations correlate well with wear of retrieved components [30].

All metallic implants, regardless of their composition, release finite amounts of metal into the surrounding tissues by a variety of mechanisms [63]. There is an increasing recognition that elevated levels of these degradation products have both local and systemic biologic implications for the patient and may lead to a range of adverse biological reactions including local soft tissue toxicity, bone loss, and an array of systemic and immunologic effects. Metal hypersensitivity responses can also cause similar reactions in the absence of high wear [19]. Furthermore, corrosion at modular junctions in orthopaedic implants can lead to release of metal debris that in many cases may be the primary source of metal release [22, 23]. A vast

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amount of effort has gone into understanding these effects in the past decade, and the orthopaedic community is just beginning to understand their scope.

In this chapter, we review the available evidence on the biological implications of metal hypersensitivity and of metal particles and ions released from MoM bearing surfaces as well as from nonarticular sources. In addition, the potential role of metal debris-induced immunologic and cellular responses in the pathogenesis of these reactions is outlined to the extent that it is understood.

Elevated Metal Ion Levels

The majority of research on MoM bearings has focused on cobalt (Co) and chromium (Cr), since molybdenum, nickel, and other trace elements do not seem to be present in sufficient amounts to elicit adverse immunologic responses. Published reports of modern MoM bearings have uniformly demonstrated higher serum or whole blood Co and Cr levels when compared to healthy controls [5, 62, 99, 115, 114, 135], as well as in comparison to total hip arthroplasty (THA) patients with ceramic or polyethylene bearing surfaces [5, 14, 108, 114]. Prospectively collected data have also confirmed higher serum levels after implantation of an MoM bearing when compared to preoperative values in the same patient [8, 14, 26, 35]. Some studies have described an initial run-in wear phase reflected by a higher serum ion concentration following implantation [8, 26, 125], while others have failed to demonstrate this phenomenon [14].

In addition to elevated ion levels in the serum and blood, metal ions are also elevated in erythrocytes of patients with MoM bearings compared with preoperative values [35] and when compared to patients with MoP bearings [82]. Several studies have reported elevated metal ion levels in the urine of patients with MoM bearings [26, 35, 62, 82, 115]. In addition, results of a recent study examining semen samples in a small group of men of child-fathering age suggest that these ions also cross into the seminal plasma, although not in significant quantities to affect the sperm parameters measured [101]. The biologic implications of these findings are unknown at this time.

Risk Factors for Elevated Ion Levels

The amount of wear, and consequently the number of metal particles and ions released into the body, has been shown to correlate with a number of variables. Interestingly, activity level has not been found to correlate with metal ion release, as might otherwise be presumed [28, 56, 108, 125].

Acetabular cup position is an extremely sensitive variable, with malpositioned cups leading to significantly more wear and ion release [28, 31, 52, 53, 50, 75, 76, 77, 125]. Head size has also been correlated with metal ion release in patients with surface

replacements, with smaller diameter heads typically associated with higher ion levels [31, 75, 76, 77]. The data regarding the effect of head size on metal ion levels in MoM THA is less clear [5, 10, 13]. Additionally, factors such as metallurgy, implant geometry (including diametrical clearance, sphericity, roughness, and coverage arc) [44], and lubrication [80] can affect the debris burden in MoM devices.

Numerous studies have been designed to compare wear and metal ion release between MoM THA and hip resurfacing devices. In a prospective randomized clinical trial, Garbuz et al. demonstrated greater elevations in serum Co (46-fold vs. 10-fold) and Cr (10-fold vs. 2.6-fold) ion levels among patients receiving large-head MoM THA compared to those who underwent resurfacing arthroplasty [39], although this has not consistently been observed in other studies [5, 25, 98, 99, 126, 135]. Further complicating the issue, the literature has shown that individual devices of the same type can perform quite differently [109, 118]. The most clear case example is the higher rate of early failures of articular surface replacement (ASR) compared to other resurfacing devices [77, 78], which has been shown to be more sensitive to malpositioning than other devices [76]. Unfortunately, this variability between devices of the same type can make interpretation of the literature difficult.

Non-Articular Sources of Metal Ions and Debris

In addition to MoM bearing surfaces, metal debris and ions can be released from other sources with the potential to produce similar clinical findings. Extensive soft tissue reactions from metallosis have been described in cases where the femoral head was able to articulate with the acetabular shell in cases of dissociation of the polyethylene liner [29, 132] or from wear-through of femoral head [68, 88]. Third-body wear can also lead to extensive metallosis [92, 93, 96].

The head–neck junction in modular femoral stems can also be a potential source of metal degradation products. In a prospective, longitudinal study of patients with well-functioning MoP THAs, Jacobs et al. documented increased metal ion levels compared to controls, hypothesizing the likely source of these increased ions to be the modular head–neck junction [63]. Subsequent case reports documented increased metal ion levels associated with corrosion of the taper at the head–neck junction [90, 81, 130], while a larger case series demonstrated head–neck corrosion led to elevated levels of Co and Cr ions, with a differential elevation in the serum Co level [22]. The head–neck taper has also been implicated as an important additional factor in metal ion release and subsequent failure of MoM THAs [39, 78]; the authors of these studies also found that Co levels were raised in preference to Cr in these cases.

Dual-taper stems (Fig. 8.1) that feature an additional modular neck–body junction also have the potential to release metal degradation products, and designs that feature a modular Co–Cr-alloy neck have recently been associated with elevated serum Co and Cr levels [23, 41].

Fig. 8.1 A dual-tapered stem design featuring an exchangeable modular neck

Adverse Local Soft Tissue Reactions

Local periprosthetic soft tissue lesions associated with metal release from orthopaedic devices can present as solid or cystic masses of variable size with associated soft tissue edema, muscle damage and soft tissue necrosis, and potential compression of nearby neurovascular or lymphatic structures. These have been described by various authors as aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL) [133], metallosis [70], and pseudotumors [105] but there is currently no clear consensus in the literature as to when or how these terms are used. The terms "adverse local tissue reactions" (ALTR) [117], and "adverse reaction to metal debris" (ARMD) [77] have been recently introduced as umbrella terms to describe these local biologic reactions.

The incidence of symptomatic ALTR in patients with MoM bearings has been widely studied. Following resurfacing, it has ranged from 0.15 to 4.0 % at a maximum mean follow-up of 8 years [20, 42, 77, 78, 87], and from 0 to 6.0 % at a maximum mean follow-up of 10.8 years following MoM THA [36, 70, 77, 97, 100, 112].

Fig. 8.2 Light microscopy photograph demonstrating extensive corrosion at the neck–body junction of a modular Co–Cr neck device from a dual-tapered stem

The incidence of "asymptomatic" ALTR has been estimated at 4.4 % at a mean 61-month-follow-up in 201 hips monitored with ultrasound or MRI [73]. Troubling is the finding that the incidence of symptomatic ALTR appears to increase with time [42], with recent reports documenting the prevalence of "asymptomatic" pseudotumor to range from 32 to 61 % [54, 134].

As discussed previously, certain implants are associated with higher levels of metal ion release, so it is not surprising they also demonstrate higher rates of soft tissue reactions. The ASR THA demonstrated an incidence of 6 % of ALTR at a mean of 41 months [77], which has risen to 48.8 % at 6 years [79]. An MRI-based study of the same device demonstrated 36 % of ASR hips (mixed group of THA and resurfacings) had features typical of a MoM reaction, and 14 % of the overall group underwent revision surgery [66].

Notably, similar soft tissue reactions have also been reported in association with corrosion at the modular head–neck taper in patients with MoP bearings [22, 81, 94, 121, 130] and in patients with dual-modular stems with a modular Co–Cr neck and a MoP or ceramic-on-polyethylene bearing surface (Fig. 8.2) [23, 69, 41]. Taper corrosion has also been demonstrated in soft tissue reactions associated with MoM bearings with little wear at the bearing surface [33, 79], suggesting that taper corrosion can release sufficient amounts of metal debris to produce similar ALTR in some patients.

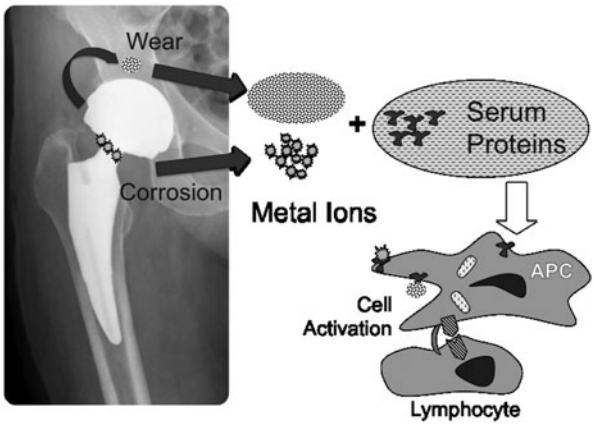

Fig. 8.3 Diagram indicating potential articular and nonarticular sources for metal ions and debris. These cause a cascade of events that activate T lymphocytes, resulting in an inflammatory response in the local periprosthetic soft tissues. *APC* antigen-presenting cell

Etiology of Adverse Local Soft Tissue Reactions

Abnormal soft tissue reactions have generally been attributed to excess metal debris, increased blood metal ions, and debris-related cytotoxicity [19, 72, 77, 78]. Deposition of Co and Cr debris within the periprosthetic tissue has been shown to induce extensive coagulation necrosis and inflammatory changes, including a macrophage and T lymphocyte response (Fig. 8.3) [85]. The mechanism responsible for this necrosis likely occurs after metal debris particles are phagocytosed by macrophages or giant cells; once in the acidic intramedullary environment of the lysosome, these particles are subject to corrosion, producing high intracellular levels of these ions which can result in cell death [45]. Extensive necrotic changes with fibrin exudation have been documented in several histological studies of failed MoM bearings [7, 85, 133], and multiple histological studies have documented the inflammatory changes seen in these reactions. Common findings have included diffuse and perivascular lymphocytic infiltration with perivascular cuffing [7, 27, 85, 133, 136] and accumulation of macrophages containing metal debris particles (Fig. 8.4) [27, 85, 133, 136]. The perivascular lymphocytic infiltrates typically consisted of CD20-positive B lymphocytes and CD3-positive T lymphocytes [85, 133, 136], with the latter typically predominating.

Although ALTR findings are most frequently seen in cases with high wear and metal ion release, ALTRs have also been described in patients with documented low wear rates [78, 19]. In these patients, it has been suggested that a metal hypersensitivity reaction, rather than wear-related cytotoxicity, may be responsible for the findings. A histological study confirmed findings more suggestive of hypersensitivity (more lymphocytes and fewer macrophages, less integrity of the synovial lining, and less normal tissue organization with perivascular lymphocytic aggregates and large acellular zones) in revisions performed with little wear when compared to a group of patients with higher wear rates [19]. Findings consistent with hypersensitivity have been described in other histological studies [85, 97, 133] and this may represent a

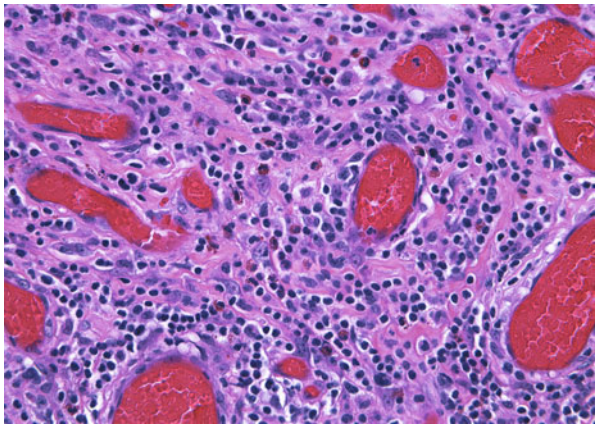

Fig. 8.4 Specimen of the hip pseudocapsule from a patient revised for an adverse local tissue reaction. Viable areas of the pseudocapsule show chronic inflammation dominated by diffuse and perivascular lymphocytes, and scattered eosinophils. Hematoxylin and eosin stain. X400 magnification

different pathway to similar clinical and radiographic findings, and may explain some of the variability in the histological findings. Metal degradation products can activate the immune system by acting as haptens, which, with their associated ligands, are potential antigens that may elicit the hypersensitivity response [46, 48].

Periprosthetic Osteolysis and Effects of Metal Debris on Bone

Periprosthetic osteolysis is among the leading causes of failure in THA, and is most often attributable to polyethylene wear from the bearing surface [12, 86]. However, both metal reactivity and metal sensitivity can lead to periprosthetic osteolysis and loosening. Although most clinical studies of contemporary MoM prostheses have not demonstrated osteolysis to be problematic with these devices, several have documented its presence. A retrospective review of 169 MoM THAs demonstrated a 5.9 % incidence of radiographic osteolysis at a mean follow-up of 27.2 months [107]. In this study, there was a significant association between early osteolysis and hypersensitivity to Co, and histological examination demonstrated perivascular accumulations of CD3-positive T cells and CD-68 positive macrophages without accumulation of significant metal debris. A post mortem study of nine MoM THAs demonstrated focal areas of osteolysis, which was often undetected by radiographs [59]. Osteolysis has also been observed in clinical studies of other MoM devices [9, 57, 70, 97].

The effects of acute and chronic exposure to Co and Cr ions on human osteoblast and osteoclast formation and function have been recently examined by Andrews et al. [3]; the authors of this study found Cr ions reduced osteoblast survival and function at clinically relevant concentrations. Osteoclasts were even more sensitive to metal ion exposure, with Co and Cr ions within the clinical range of patients with MoM bearings reducing both cell number and resorption in mature osteoclasts. Another in vitro study demonstrated that osteoblastic activity is impaired following phagocytosis of metal particles, which can contribute to cellular events occurring during aseptic loosening

and soft tissue destruction [82]. Other studies have confirmed high concentrations of Co and Cr ions are toxic to osteoblasts and reduce cell activity [4, 38, 131].

Effects on the Host Immune System

Metal debris can modulate the activities of the immune system by a variety of stimulatory and suppressive mechanisms. Macrophage activation is stimulated by the presence of Co and Cr nanoparticles, which leads to secretion of proinflammatory molecules (IL-1β, TNFα, IL-6, and IL-8); these particles can also upregulate transcription factor NF-κB and downstream proinflammatory cytokines [1, 19]. A recent study demonstrated metallic debris can induce a proinflammatory response in macrophages through an inflammasome multiprotein complex in a concentration-dependent manner [16]; inflammasome activation produces IL-1β that activates NF-κB through a feedback loop, resulting in production of other proinflammatory cytokines. Patients with elevated serum metal ion levels have also been found to have significantly elevated lymphocyte reactivity [47].

Reduced peripheral lymphocyte counts (both B and particularly T lymphocytes) have been found following MoM hip replacements [49, 50, 83, 102]. Covariance analysis in one of these studies determined the variation in peripheral lymphocyte count could be accounted for by circulating metal ion (particularly cobalt) levels [50]. The mechanism behind reduced peripheral lymphocyte numbers may be due to direct cytotoxicity from metal particles [2] or to reduced proliferation of T cells [2, 102]. The clinical effects of reduced lymphocyte counts in patients with MoM bearings have not been clearly elucidated.

Metal degradation products have also been shown to activate the immune system by forming metal–protein complexes, which potentially serve as antigens for eliciting hypersensitivity [27, 46, 65, 91]. These complexes have been shown to induce lymphocyte activation through proliferative responses, although the mechanism by which this activation occurs remains unknown.

Circulating metal ions may also play a role in the host's ability to fight infection [58]. A recent study by Anwar et al. demonstrated MoM debris accelerated bacterial growth [6]; these authors hypothesized the aggregated particulate debris promoted bacterial growth by providing a scaffold on which biofilm could grow.

Systemic Effects of Metal Debris

Cobalt toxicity can produce various symptoms such as polycythemia, hypothyroidism, cardiomyopathy, carcinogenesis, and neuropathy; and chromium toxicity can have effects such as neuropathy, carcinogenesis, and hypersensitivity [89, 116, 61]. While these constituents of orthopaedic implants have known toxicities, it should be pointed out that these generally refer to soluble forms of the

metallic elements and may not reflect the toxicity profile of the specific metal degradation products of orthopaedic implants, whose precise chemical composition has yet to be defined.

A number of systemic effects of metal ion release from orthopaedic devices have been described, mostly in the form of isolated case reports. A recent case from Italy demonstrated progressive and complete visual and hearing loss in the setting of elevated metal ion levels, which partially resolved with resection arthroplasty of the MoM bearing [111]. Another case from Japan was described with progressive sensory disturbances, hearing loss, and biopsy-proven axonopathy in association with a poorly functioning MoM prosthesis with elevated ion levels [61]. Others have described similar progressive visual or auditory deficits in the setting of elevated metal ion levels [120, 124]. Hypothyroidism [61, 103], peripheral neuropathy [61, 103, 111], cardiac manifestations [103, 124], and varied other neurologic manifestations [89, 124] have also been described in the setting of elevated metal ion levels or metallosis, although all in isolated case reports or small case series. The available literature is insufficient to understand the scope of these findings, although it is likely that many systemic effects have gone undiagnosed or unreported.

Although MoM bearings are not recommended for patients with renal insufficiency due to decreased renal clearance of metal ions [60], the literature to date has not demonstrated additional nephrotoxicity from MoM devices [24, 8].

Teratogenesis

The teratogenic potential of MoM debris is an important consideration, particularly as these bearings have been advocated for and used in younger patients due to their purported excellent wear properties. Although there is little evidence of its impact on human embryos, metal ion exposure has been shown to be teratogenic in multiple animal studies [40, 67]. Two studies have examined transplacental transfer of metal ions from maternal to fetal blood and reported conflicting results [15, 137]; although there is suggestion these ions can be transferred at birth, neither of the studies examined women with abnormally elevated ion levels or poorly performing implants. Furthermore, concern exists over DNA damage and chromosomal aberrations in patients with MoM bearings and the risk of passing these to the next generation [32, 74, 106, 113], as it was recently found that Co and Cr particles can cause DNA damage across a cellular barrier [11]. Given the limited data on potential teratogenicity of MoM bearings, it can be concluded that although a theoretical risk exists, there remains insufficient clinical data to confirm this as a concern in humans.

Carcinogenesis

Large meta-analyses and population-based studies have not demonstrated an overall increase in cancer after joint replacement [104, 119, 129]. A literature review performed in 2001 documented at least 25 cases of malignancy occurring with total

joint prostheses [129], but concluded that a causal link could not be established between the prosthesis and the development of cancer. However, these studies did not take into account the type of implant or dose of metal ion exposure, and the mean follow-up has been shorter than the latency for some types of tumors.

Animal models have documented the carcinogenic potential of metal ions [55, 95, 122]. In a large population-based study in Finland, patients with MoM bearings were found to have a higher rate of leukemia (3.77-fold) when compared to patients with MoP bearings, although this difference was not found to be statistically significant with the numbers available [127]. A more recent study by the same group found patients with a specific earlier design of MoM THA had a higher mortality due to cancer than those with a MoP THA (standardized mortality ratio 1.01:0.66, respectively) during the first 20 years postoperatively, but not thereafter [128]. Due to insufficient follow-up, as well as insufficient data regarding dose-response, population bias, and confounding variables, no conclusion can be reached based upon the available data that there is a causal link between MoM bearings and the development of cancer in humans. However, such an association cannot be ruled out because of these limitations.

Conclusions

Although a large majority of patients who have undergone MoM hip arthroplasty have had satisfactory clinical results, MoM bearings can have a range of potential deleterious local and systemic effects on the host, through both the innate and adaptive immune system. The potential for MoM bearings to induce a biological response is based, in large part, upon the amount of metal ions and particulate debris released, either from the bearing surface or from modular metal–metal taper junctions. Adaptive immunity may play an important role in the pathogenesis of these adverse soft tissue reactions, but current diagnostic tools such as patch testing and lymphocyte transformation testing have yet to be clinically validated in a robust fashion.

Although these adverse biologic responses to metallic implants are uncommon, surgeons should carefully consider the risks and benefits of decisions they make in an effort to improve the outcomes of patients. Optimization of MoM bearings and modular taper junctions to further diminish wear and corrosion is highly desirable.

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Chapter 9
What Does the Histology Tell Us?

Thomas W. Bauer

Introduction

There are several different biologically based mechanisms whereby a hip arthroplasty of any composition can fail. Those mechanisms include, among other things: (1) failure to achieve adequate initial bone bonding, (2) fatigue failure at the bone–implant interface, (3) particle-induced bone resorption ("osteolysis"), (4) infection, and (5) other adverse tissue reaction. The histology of tissue samples obtained from around a failed device can often provide us with important clues about the dominant mechanism of failure in any given case.

For example, tissue samples obtained adjacent to an implant that either failed to achieve adequate initial fixation or underwent fatigue failure of a marginally bonded bone–implant interface often reflect the consequences of implant motion [1, 2]. Those features include primarily a proliferation of small blood vessels (granulation tissue) and fibrosis (Fig. 9.1). Macrophages, particles of wear debris, giant cells, lymphocytes and plasma cells are rare, and neutrophils are absent. The fibrous membrane can create a linear radiolucency around the implant; and although one might argue that this is one type of adverse tissue reaction, it represents the consequence of motion, not a reaction to particles, bacteria, toxins, or antigens.

Tissue around an implant that has loosened because of particle-induced bone resorption contains areas of necrosis as well as a high concentration of macrophages, many of which contain particles. The particles reflect the composition of the device, and therefore can be composed of polyethylene, metal, barium sulfate (added as radiographic contrast media in some types of bone cement), zirconia (added as radiographic contrast media in other types of bone cement), alumina, or other compounds. Lymphocytes are usually relatively low in number [3], and when present commonly perivascular in location. Fibrous membranes that contain extensive metal debris are sometimes referred to as showing "metallosis," a term that has been used with reference to either the gross or the histologic appearance of the membrane (Fig. 9.2).

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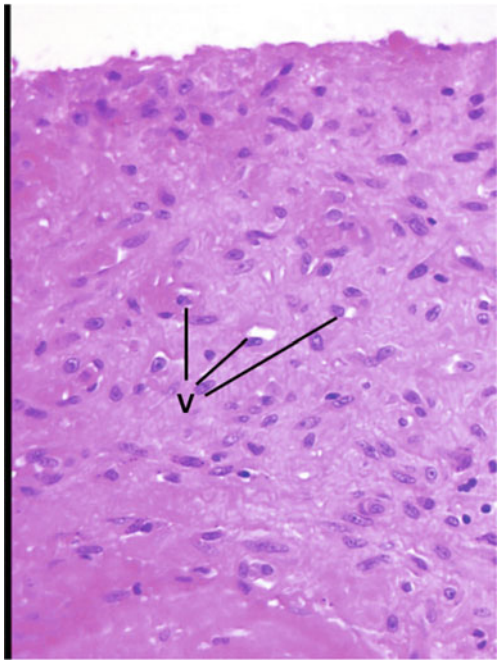

Fig. 9.1 Fibrous membrane with granulation tissue from around an acetabular component that failed to achieve adequate initial fixation. The radiolucent membrane was several millimeters thick, and lacks a significant number of macrophages. No particles of debris are evident and there is neither acute nor chronic inflammation. Numerous small blood vessels (*V*) are present. Hematoxylin and eosin (H&E)

Tissue around an implant that has failed because of infection contains neutrophils [4]. Particles and macrophages may also be present, but if the membrane contains more than five neutrophils (polymorphonuclear leukocytes, PMNs) in each of five or more high-power (40X) microscopic fields [5], then the dominant mechanism of failure is most likely infection, not particle-induced bone resorption. In the histology of periprosthetic tissues, neutrophils "trump" macrophages. Neither mechanical loosening, nor particle-induced osteolysis induces acute inflammation. Lymphocytes, plasma cells, and surface necrosis are also commonly present around infected, or previously infected implants (see below), especially at the second stage of a 2-stage revision for infection, but in the appropriate clinical context, when neutrophils are present, we can diagnose active infection with a relatively high degree of certainty.

ALVAL

However, the histology of most relevance for this chapter is periimplant tissue that is characterized, most importantly, by a laminated appearance, with a superficial layer of necrosis, and underlying layers of sclerotic, hyalinized fibrous tissue with diffusely distributed as well as perivascular lymphocytes (Figs. 9.3 and 9.4). Individual features of this appearance are not specific for failed metal–metal implants [6], but the combination is characteristic of a subset of failed metal–metal implants. First emphasized by Willert and coworkers [7, 8], the combination of a thick layer of

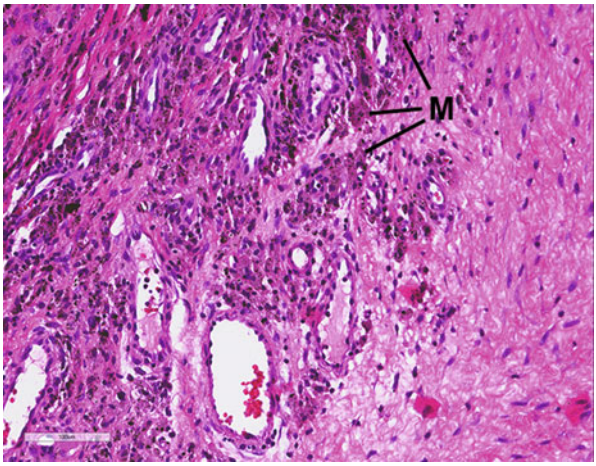

Fig. 9.2 This fibrous membrane was obtained from around a failed hip and is characterized by numerous macrophages (*M*) containing countless opaque particles. Additional analytical studies are necessary to determine the content of those particles with certainty, but the particles are morphologically quite consistent with metal debris. Sometimes characterized as "metallosis," there are few lymphocytes or plasma cells present and there is no acute inflammation. The macrophage reaction represents a manifestation of the "innate" response to debris particles and does not show features of a well-developed adaptive immune response

necrosis over chronic inflammation with perivascular lymphocytes and blue-green debris particles in macrophages was associated with failed metal–metal implants and was called "ALVAL: Aseptic Lymphocyte-dominated Vasculitis-Associated Lesion."

As noted above, none of the individual features of ALVAL are specific for failed metal–metal implants [6]. Variable degrees of necrosis are commonly found in cases of particle-induced osteolysis, diffuse chronic inflammation is common at the second stage reconstruction of a 2-stage operation for known infection as well as in patients with an underlying inflammatory arthropathy, and perivascular lymphocytes are very common at primary arthroplasty (Fig. 9.5), so none of these morphologic features should, in isolation, be used to morphologically diagnose a hypersensitivity reaction to an implant. However, the combination of necrosis, extensive, diffuse chronic inflammation, and marked perivascular lymphocytes, especially when distributed in a distinctly laminated way, is characteristic of some cases of failed metal–metal arthroplasty and suggests an immunologic reaction (see below).

The Histology of Hypersensitivity Reactions in General

The immune response to external antigens can take several different forms, and hypersensitivity reactions in general have been grouped into four categories [9]:

Immediate hypersensitivity (Type I) occurs within minutes of exposure to an antigen, and is a complex reaction that involves TH2-type helper T-lymphocytes that

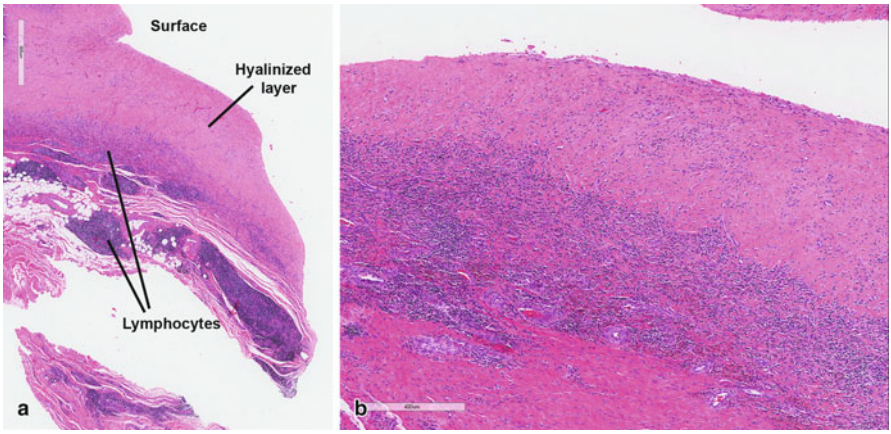

Fig. 9.3 **a** Low magnification of a membrane around a failed metal–metal hip. There is minimal necrosis in this visual field, but the laminated appearance in which a layer of hyalinized fibrous tissue overlies diffuse and perivascular lymphocytes are typical of "ALVAL." **b** This higher magnification shows diffuse chronic inflammation at the lower border of the hyalinized layer. The suggestion of brownish pigment reflects particles in macrophages

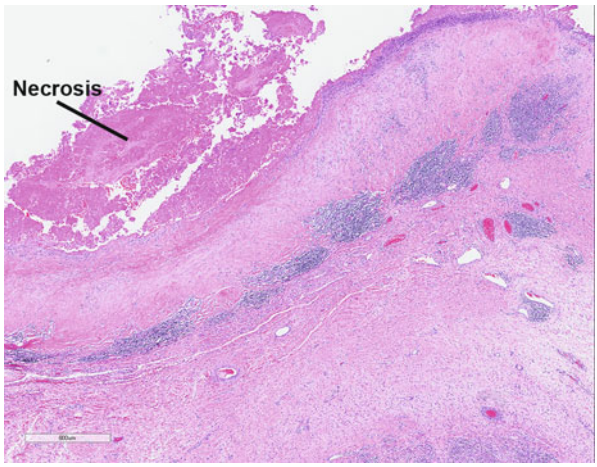

Fig. 9.4 Low magnification of another example of "ALVAL" in which superficial fibrin and necrotic tissue overlie layers of hyalinized fibrous tissue, diffuse, and perivascular chronic inflammation

promote IgE secretion from B lymphocytes, rapid release of vasoactive cytokines from mast cells, and accumulation of eosinophils and other inflammatory cells at the sites of antigen deposition. Clinical examples of Type I hypersensitivity include allergic rhinitis, some types of asthma, and systemic anaphylaxis. Although tissues from some patients with failed implants contain abnormally high concentrations of eosinophils, this has not been a consistent finding and is currently of unknown clinical significance. In general, Type I hypersensitivity is not thought to be a major mechanism of arthroplasty failure.

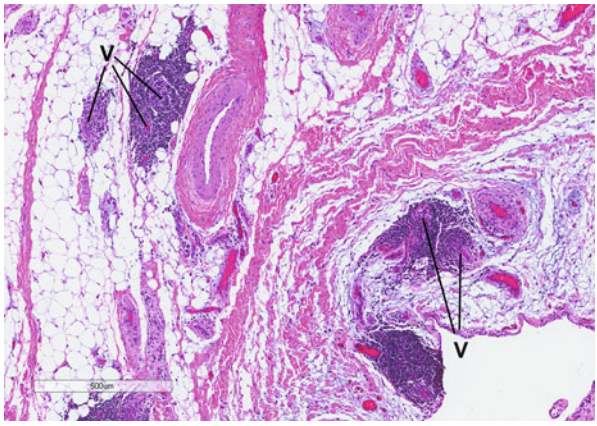

Fig. 9.5 Perivascular (*V*) lymphocytes are commonly found in synovial tissue at the time of primary arthroplasty, as illustrated in this figure. Their significance in that setting is unknown, although it is often attributed to a subclinical drug reaction

Antibody-Mediated Hypersensitivity (Type II), involves immunoglobulins that are either directed against specific antigens (usually on the surface of target cells), or are directed against soluble factors that secondarily bind to cell surfaces. Once antibodies are attached to the surface of the target, destruction can be mediated by macrophages (via phagocytosis), neutrophils, natural killer lymphocytes, or other cells. Clinical examples of Type II hypersensitivity include transfusion reactions, some types of autoimmune disorders, and some types of drug reactions. Opsonization of particles of wear debris may involve immunoglobulins as well as other proteins, and one might speculate that variability in the opsonization process and recognition of opsonized particles by macrophages could in part explain the variable inflammatory reaction among patients exposed to similar doses of debris particles. Although plasma cells are seen in some cases of aseptic loosening [3] as well as in some cases of ALVAL [5], the extent to which immunoglobulins participate in aseptic loosening is unknown.

Immune-Complex-Mediated Hypersensitivity (Type III) is the consequence of an inflammatory reaction to immune complexes deposited in tissues, usually blood vessels. Antibodies and antigens commonly form complexes in vivo, but only selected immune complexes become pathogenic for reasons that are not well understood. Factors thought to influence the extent to which immune complexes may damage tissues include the size of the complex, the ability of the mononuclear phagocytic system to remove complexes from circulation (for example, in the spleen), the charge and valence of the antigen, and the proportion of molecules within the antigen-antibody complex. Pathogenic immune complexes are often deposited in vessels of, for example, the kidney or synovium, and induce inflammation and complement fixation. Morphologic manifestations of Type III hypersensitivity usually include acute, necrotizing vasculitis with neutrophils and fibrinoid necrosis of the vascular wall. Although perivascular lymphocytes are one of the features of ALVAL, actual necrotizing vasculitis with neutrophils is not usually seen (see additional comments below). Clinical examples of Type III hypersensitivity include several types of glomerulonephritis, systemic lupus erythematosus, and polyarteritis nodosa.

Cell-Mediated Hypersensitivity (Type IV) is the most important immunologic response to many infectious agents, is an important component of tumor immunity, mediates contact dermatitis and many autoimmune diseases, and is probably the most important mechanism of transplant organ rejection. T-lymphocytes that have been activated by antigens mediate a complex inflammatory reaction that often includes several subtypes of lymphocytes and macrophages. CD4+ T-cells recognize an antigen (commonly on the surface of antigen-presenting cells), differentiate into TH-1 cells and secrete cytokines, including IL-12, TNF, IFN-γ, and others. These cytokines recruit and promote differentiation of inflammatory cells, activate macrophages, and indirectly increase vascular permeability. In response to some types of antigens, macrophages develop an "epithelioid" morphology and along with lymphocytes and occasional giant cells form more or less spheral aggregates as granulomas. While "immune granulomas" are typical of the inflammatory reaction to some types of infections (especially mycobacteria), morphologically similar granulomas can develop as an innate (nonspecific) inflammatory reaction to particles of wear debris. It is unclear why in some patients the macrophage reaction to particles of debris attains an epithelioid, granulomatous morphology while in other patients the macrophages are easily identified but do not become well-formed granulomas. As described in more detail below, tissue around some failed metal–metal hips is dominated by macrophages with debris particles (metallosis) without features of hypersensitivity, but in other cases of failed metal-metal implants, the high concentrations of diffuse and perivascular lymphocytes more strongly supports a type of hypersensitivity reaction (adaptive immune response).

Not All Metal–Metal Hips Fail Because of ALVAL

Although the combination of morphologic findings now known as ALVAL are characteristic of some failed metal–metal implants, not all failed metal–metal implants show all of the features of ALVAL. Some cases of failed metal–metal hips show fibrous membranes with essentially no inflammation and minimal macrophages or debris. In the appropriate clinical context, these arthroplasties may have failed for a reason unrelated to an immune response, such as insufficient primary fixation or fatigue failure at the bone–implant interface of a marginally ingrown device. Tissue samples from other cases lack lymphocytes and necrosis, but have a very high tissue concentration of macrophages with particles consistent with metal. While the metal particles are sometimes opaque (appearing black in H&E stained sections), sometimes the particles have a grey, or almost light green color, perhaps the consequence of corrosion (Fig. 9.6). In these examples of "metallosis," the dominant mechanism of failure may have been an innate biologic response to wear debris via mechanisms similar to those seen in nonmetal–metal hips rather than an adaptive immune response. Finally, tissue around a failed metal–metal implant may contain acute inflammation characterized by neutrophils (Fig. 9.7). When the maximum tissue concentration of neutrophils reaches five or more neutrophils in each of five or

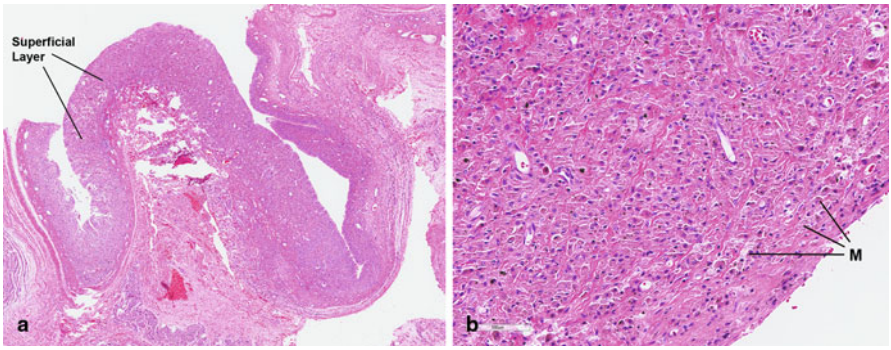

Fig. 9.6 **a** The periprosthetic tissue in this case of failed metal–metal hip shows a few, but not all of the features of "ALVAL." There is a suggestion of a lamination, but there is no superficial necrosis; the membrane does not show hyalinization and there is minimal diffuse or perivascular chronic inflammation. A thick layer of macrophages is evident. **b** Higher magnification shows that the macrophages (*M*) contain brown/grey appearing particles. There are virtually no lymphocytes. This membrane is probably best characterized as "metallosis," and does not show histologic features that suggest an immune reaction

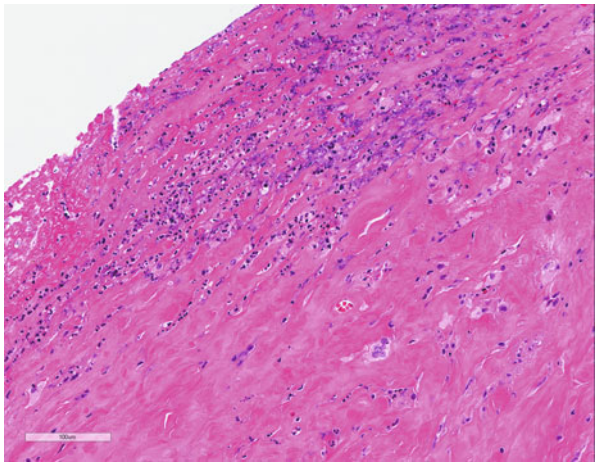

Fig. 9.7 Fibrous membrane from a painful metal–metal hip prosthesis. The surface of the hyalinized layer contains numerous neutrophils. This acute inflammation strongly suggests infection, and in the appropriate clinical context may indicate that the dominant mechanism of morbidity in this case is a periprosthetic infection

more high-power fields, then we interpret the morphologic findings as suggestive of infection. Several different modes of failure can be present in any given arthroplasty, but in the appropriate clinical context, a high concentration of neutrophils strongly suggests infection regardless of the presence or absence of features of ALVAL.

It should also be noted that tissue around some failed metal–metal devices may show only limited components of the overall ALVAL picture. For example, the laminated appearance of the membrane may be evident without the diffuse chronic inflammation, or one may find striking diffuse and perivascular inflammation without surface necrosis. Recognizing this variability in morphologic appearance Campbell and coworkers have described a grading, or scoring system in which numerical values

are assigned to specific features [10]. Accepting that ALVAL represents an adaptive immune reaction, a high ALVAL score would more strongly support that immune response, whereas a low score might more strongly support a different dominant mechanism of failure, such as the innate macrophage reaction to wear debris ("metallosis"), mechanical factors, etc. While the Campbell ALVAL scoring system itself has not been widely adopted, the concept of grading either individual morphologic features of ALVAL (for example, perivascular lymphocytes), or combining some combination of those features into a single grade should help sort out the degree to which these morphologic findings reflect underlying mechanisms of arthroplasty failure.

Pseudotumors (Inflammatory Pseudotumors)

Besides a thickened joint capsule with histologic features consistent with ALVAL, surgeons, radiologists, and pathologists have described some cases of metal–metal arthroplasty in which one or more soft tissue masses, cysts, or cystic masses have developed. These mass lesions can be associated with an effusion, and can be destructive of adjacent normal tissue [11–13]. Inflammatory masses of uncertain pathogenesis composed of lymphocytes and plasma cells located in the mediastinum, retroperitoneum, and elsewhere have been recognized for many years [14]. In those locations and when not associated with orthopedic devices, the lesions often resolve spontaneously. The same term has been used to describe inflammatory mass lesions associated with failed total joint prostheses [15]. In 2008, Pandit and coauthors [11] described 17 women patients with painful hips related to metal–metal hip resurfacing implants who were found to have soft tissue masses with or without cysts or effusions. Described as pseudotumors, these masses contained necrosis, some contained metal debris, and many contained macrophages and lymphocytes, especially diffuse chronic inflammation. The same group [12] studied the histologic features of pseudotumors in four patients with bilateral metal–metal resurfacing hip implants. The masses were partially solid and partly cystic, and contained granulomatous inflammation along with lymphocytes with phenotypic markers consistent with a Type IV hypersensitivity reaction. Campbell and coworkers evaluated tissue from 32 failed metal–metal hips that had been associated with pseudotumor-like lesions, including "soft tissue masses," "enlarged bursas," or "cysts" [10]. The ALVAL scoring system, mentioned previously, was used in an attempt to grade the various histologic features described above. The extent of wear from the retrieved implants was also evaluated. In general, the tissues of patients who had undergone revision for high wear tended more to show metallosis (macrophages and metal particles with fewer lymphocytes) than patients who presented with pain and were clinically suspected of having metal sensitivity. The latter group of patients had higher ALVAL scores (e.g., more necrosis and chronic inflammation). The ambiguity inherent in the term "pseudotumor" has allowed its application to a variety of lesions that might or might not be inflammatory in origin. For example, in one study that described pseudotumors in patients with well-functioning metal–metal hips, cystic lesions with a wall thickness even less

than 2 mm were classified as “thin-walled pseudotumors” [16]. Other authors limit use of the term “inflammatory pseudotumor” to mass lesions with histologic features consistent with ALVAL [12].

Another unresolved problem with respect to implant failure is the role of low-grade chronic infections. As noted above, tissues excised from around antibiotic spacers at the second stage of a two-stage operation for known infection sometimes contain extensive necrosis, diffuse and perivascular inflammation. In these cases, the antigen cannot be metal, but the inflammation more likely reflects an immune reaction to either bacteria (viable or necrotic), bone cement, or antibiotic. Other patients with non metal–metal implants but with clinical features suggestive of infection may demonstrate a similar histologic picture. These observations raise the question of very low-grade chronic infection in some metal–metal arthroplasty patients who have extensive chronic inflammation in periimplant tissues, along with other findings suggestive of infection (e.g., elevated erythrocyte sedimentation rate and/or C-reactive protein).

At this time, it is not clear that all of the mass lesions that have been described as pseudotumors based on intraoperative observation or preoperative imaging studies have ALVAL-like histologic features suggesting an immune reaction. Studies in which preoperative imaging, intraoperative tissue sampling, and histologic findings are correlated are needed to help sort out the relative contributions of an innate inflammatory reaction to particles from an immune reaction to particles and/or ions as well as other mechanisms of failure of these devices.

Clearly prospective studies that carefully correlate preoperative imaging findings, intraoperative observations, analytical evaluation of explanted devices, and histologic findings are needed to help sort out the relative contributions of an innate inflammatory reaction to particles from an immune reaction to particles and/or ions as well as other mechanisms of failure of these devices.

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Part IV
Biomechanics

Chapter 10
Why Metal-on-Metal: What Laboratory Tests Have Shown Us

Peter Thomas, Burkhard Summer, Marc Thomsen, Veit Krenn and Jan Philippe Kretzer

Introduction

Given the demographic changes of the populations in particular in western countries, there is an increasing demand for hip arthroplasty. Already now, more than one million artificial hip joints are implanted worldwide. Rates for primary and revision total hip arthroplasty are even outnumbering initial projections [14].

The increasing use of joint replacements in young and active patients further stresses the need of implant durability. For the selection of suitable materials, three main types of materials are used: ceramics, metals and polymers. The bearing surfaces of implants undergo friction and wear. Metal-on-metal (MoM) bearings were reintroduced in hip arthroplasty to face the issues of polyethylene wear with its potential of inflammatory tissue reactions resulting in bone loss and implant loosening. The prevalence of MoM bearings—in the form of resurfacing arthroplasty and conventional arthroplasty—was rising in part also due to their popularity amongst young and active patients. However, even patients with well-functioning MoM arthroplasty may show increased blood cobalt (Co) and chromium (Cr) levels that often reach a steady state after about 2 years. Such ion and particle release may lead to intolerance reactions including hypersensitivity. Accordingly, a spectrum of adverse local

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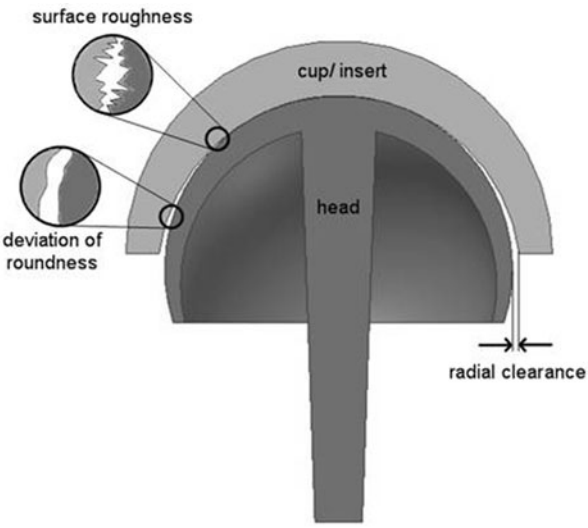

Fig. 10.1 Scheme of MoM implant. (Adapted from Kretzer P. [12])

tissue reactions to metal debris has been described and an immune response may result in complications like pain, osteolysis, loosening and—in a small number of patients—formation of so-called pseudotumors.

Aspects of Materials and Tribology

With regard to the **implant geometry,** ideally, head and cup are ball-shaped elements with slightly differing diameters. The small space between head and cup is described as radial clearance. Even under best polishing and manufacturing conditions, the surfaces are not completely spheric and smooth. Thus, the head and cup may present slight deviations of roundness. The geometric indicators for description of bearing partners include diameter, clearance, deviation of roundness and surface roughness.

Figure 10.1 shows a schematic cut through a MoM surface replacement.

When assessing **metallurgy,** the most widely used alloy in MoM implants is Co28Cr6Mo due to its good wear properties and high corrosion resistance. Traces of nickel, manganese or iron may also be included. The main manufacturing- and material-dependent criteria influencing the mechanical and metallurgical properties of hip implant bearings include: *carbon content of the alloy* (low carbon, lc, $< 0.15\,\%$; high carbon, hc, $\geq 0.15\,\%$), *primary manufacturing method* (cast or wrought) and heat treatment. The carbon content influences the formation of carbides within the matrix material, which increases toughness and wear resistance of the alloy. Using casting technique, larger "blocky" carbides are achieved that are in a size range of some hundreds of microns, whereas wrought material shows smaller carbides that are typically about one magnitude smaller compared to cased carbides.

Hip **simulator wear studies** performed in the last decade—as summarized in a meta-analysis [13]—allow the below listed statements regarding design and manufacturing related parameters and their impact on the wear of MoM bearings:

- For implants with a diameter of 36 mm and above, an increase in head size will result in less running-in wear. If lubrication is not sufficient and components are not at least partly separated by a fluid film, wear might increase due to the longer wear path. Therefore, sufficient lubrication is essential.
- A smaller clearance leads to reduced running-in wear. However, there are limits for the minimum clearance and equatorial contact has to be avoided.
- A smooth surface (low roughness) and a highly spherical geometry (low deviation on roundness) reduce wear.
- The influence of alloy carbon content remains unclear.
- The manufacturing method (wrought vs. cast) seems to not affect wear.
- Heat treatment processes increase wear, at least during the steady-state wear phase.

In general, a direct comparison of different simulator studies is difficult. This is due to the fact that wear of similar implant designs can differ significantly between different investigators. An example of such difference can be seen when directly comparing the findings of Dowson et al. [4] and Chan et al. [1], who investigated an identical implant design. Dowson et al. defined a mean running-in wear rate of 2.3 $mm^3/10^6$ cycles, whereas Chan et al. reported a running-in wear rate about one order of magnitude lower (0.24 $mm^3/10^6$ cycles). These data may explain the restrictions that apply to the comparability of wear studies from different investigators.

Many parameters add to minimising wear and improving outcomes apart from purely technical characteristics of artificial joints. Important factors encompass positioning and orientation of implant components during surgery. Wear of MoM implants increases with increasing cup inclination angle [9]. The risk of impingement (contact of implant neck with implant cup) or luxation (dislocation of the joint) is also influenced by the orientation of the implant components. Additionally, patient-specific aspects such as body weight and activity level are also assumed to impact wear. For example, Kamali et al. showed experimentally, that the gait velocity and also resting periods impact the wear performance of a MoM bearing [10].

Different **wear modes** are used to classify the wear mechanisms of artificial joints. The four wear modes depend on the bearing partners in use. The classification is independent of the bearing partner materials and is thus valid for different types of artificial joints. A schematic overview of the four modes is shown in Fig. 10.2. Mode 1 is represented by articulation of primary bearing surfaces only. Despite production of wear, this mode reflects the ideal conditions implants are designed for. Modes 2–4 stand for malfunctioning implants. In mode 2, a bearing surface articulates with a secondary non-bearing surface. Such a scenario could be found when the head of the implant (sub)luxates and then makes contact with the rim of the cup. This mode 2 can provoke massive wear and rapid failure of an artificial joint. Mode 3 represents the articulation of primary bearing surfaces in the presence of third bodies in the joint space, causing increased abrasive wear. Typical third bodies are metal particles,

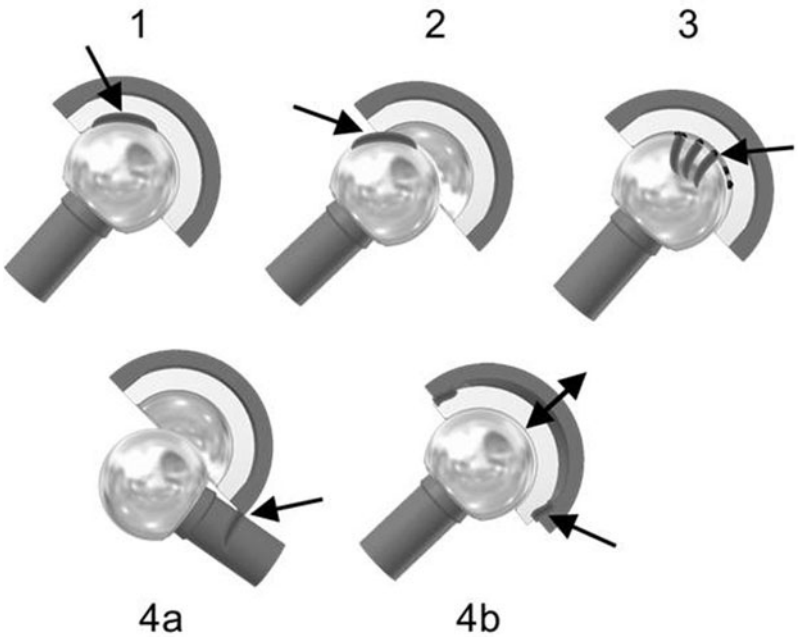

Fig. 10.2 Wear modes (*1–4*) of hip replacements, adapted from [12, 20]

ceramic fragments, bone cement and bone fragments. Third bodies can strongly enhance wear formation. Mode 4 is characterised by articulation of two non-bearing surfaces, for example as impingement or "backside" wear. Backside wear may arise from many conditions including wear between the polyethylene acetabular liner and the metal shell, fretting at the site of modular junctions, and friction between the implant stem and the surrounding bone or bone cement. Fragments and particles generated in mode 4 can reach the joint space and subsequently produce third body wear.

The Metal Ion Concern

Laboratory tests may assess a large number of parameters in accurate and reproducible manner, if standardized procedures and well-functioning laboratory equipment are applied. However, it is important that the test scenario is covering the "real situation" and that we can assign clinical significance to the test data. This general approach is also valid for MoM arthroplasty. Larsson et al. stressed the potential of disease registries to use outcome data amongst others for learning about the significance of laboratory and clinical data [16]. For example, analysis of data from the national joint registries for England and Wales—as reported by Smith A. J. et al.—showed that (1) hip resurfacings only resulted in similar survivorship

to other surgical options in men with large femoral heads, and (2) inferior implant survivorship occurred particularly in women [22]. From a clinical point of view, asymptomatic patients with MoM arthroplasty may also have suboptimal component position and elevated blood ion levels so that an algorithmic approach to diagnosis and management of MoM arthroplasty was suggested [18].

Blood/serum ion levels reflect systemic exposure to metal ions and implicate also local exposure to corrosion products. However, the extent of such exposure is not showing a linear or direct relation to the potential of local adverse tissue reactions. The rare solid pseudotumors are mostly observed with resurfacing procedures—in particular in women. In 2010 Delaunay et al. stated that "... MoM bearing couples are contraindicated in cases of metal allergies or end stage renal dysfunction and small size resurfacing should cautiously be used" [3]. Delaunay also indicated, that "the rate of circulating Co and Cr ions is low when the bearing couple functions well (Co < 1 μg/L)". In contradistinction, the ability of blood metal ion values to discriminate between well-functioning and failed hips is not well known. The British Medicines and Healthcare products Regulatory Agency (MHRA) has suggested a cut-off level of 7 parts per billion (ppb). A. J. Hart and coworkers found in a pre-revision group (mixed with matching controls with well-functioning hip) that the 7 ppb cut-off level had 89 % specificity—but only 52 % sensitivity for detecting a preoperative unexplained failed MoM hip replacement [8]. Accordingly, laboratory tests of blood metal ion level are not regarded by every orthopaedic centre to be the only significant factor in the decision of when to revise a MoM large head total hip replacement. Lingen et al. reported on 10 patients with the highest Co level (18–153 μg/L) within their over 600 patients that had received a stemmed large head MoM arthroplasty: "They were asymptomatic and without signs of neurological, cardiological, thyroid or renal dysfunction" [17]. In contrast, Langton and co-authors found in 35/40 of their patients with hip resurfacing and blood Co levels > 20 μg/L prior to revision "some degree of bone loss" [15]. Finally, in the recent European multidisciplinary consensus statement, the current recommendations for use and monitoring of MoM bearings in hip replacement differ amongst others regarding the eventual threshold level; the threshold level for clinical concern is expected to be within the range of 2–7 μg/L—but needs additional imaging [7]. Thus, laboratory testing has shown us that additional parameters—including several not yet identified patient-related factors—have to be integrated in evaluation.

This statement also applies for the assessment of **peri-implant tissue response.** Apart from the different mechanisms leading to osteolysis [19], we have to remember, that the histological picture only gives a snapshot-view on the actual stage of a dynamic peri-implant process. Krenn et al. had proposed by a consensus classification to subdivide the peri-implant tissue reaction patterns in a particle-dominated foreign body like response (Type I), a granulocyte-dominated infectious type (Type II), the mixture of Type I and II (combined type, Type III) and a paucicellular fibrotic reaction (Type IV, indifferent type) [11] (Figs. 10.3 and 10.4). Threshold levels for neutrophilic infiltrate (23 neutrophils/10 high power fields), indicative of infection, were postulated [21].

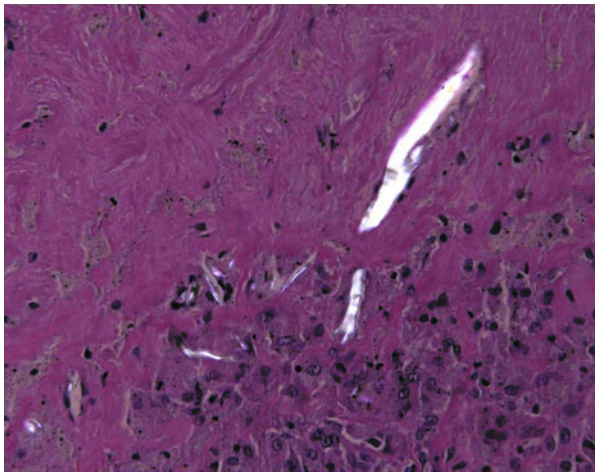

Fig. 10.3 Wear-induced inflammatory reaction, in the center polyethylene fragments (Type I reaction)

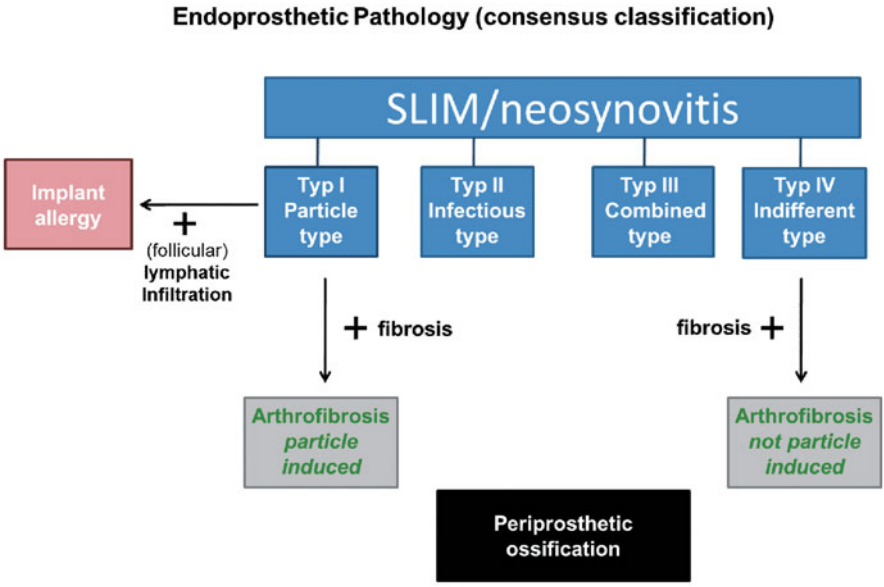

Fig. 10.4 Revised consensus classification according to Krenn et al. [11]. *SLIM* synovial-like interface membrane

Early reports had pointed to the role of lymphocyte-dominated inflammation in loosened MoM arthroplasty [2, 24]—a subtype of peri-implant reactivity, which has been included in the recent revised consensus classification [11]. Delayed type **hypersensitivity**—as reflected by positive patch test reactions and enhanced lymphocyte transformation test (LTT) reactivity to metals—was detected as a potential elicitor of failed MoM-arthroplasty in some patients [23]. Metal sensitivity could be

responsible for an overall earlier failure of arthroplasty, but laboratory test results would not always allow identification at the single patient level [5]. Hallab and co-workers pointed to the enhanced LTT reactivity to metals in many implant bearing patients [6]. However, again, further tools are needed to specify the clinical meaning of such enhanced LTT reactivity.

Conclusion and Outlook

Hip arthroplasty has evolved to one of the most frequent and successful elective surgical procedures. Since all materials and their combinations have advantages and drawbacks, a spectrum of materials is in use. Metals are rather wear and fracture resistant—but increased wear can occur especially in the case of imprecise implantation or errors in positioning of components. There is an ongoing discussion on biological effects of metal ions and particles—and risk scenarios of MoM pairing are focus of actual research. This discussion emphasizes the need of objective outcome measures, joint registries and integrated view of clinical findings to interpret the significance of laboratory test parameters.

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Chapter 11
What Do the Retrievals Really Tell Us?

Robin Pourzal, Robert M. Urban and Markus A. Wimmer

Retrieval analysis is an important tool in orthopedic research to understand the clinical performance of joint replacements [1]. Many retrieval studies have been conducted on metal-on-metal (MoM) hips, especially in the light of the recent high failure rates due to adverse local tissue reactions caused by metallic wear and corrosion products. Ideally, retrieval analysis includes the investigation of periprosthetic tissue in addition to the analysis of the artificial device. Generally, one could approach the subject in two ways and ask: "Why did the device fail?" or "Why did the device work?" [2]. In order to address the former question, devices retrieved for cause during revision surgery are an appropriate source, while for the latter, devices retrieved postmortem are more suitable [3]. It is important to not only focus on failures but also learn from the successful designs. In the case of MoM, retrieval analysis helped to gain a more fundamental understanding on why some MoM hip joints developed dissatisfying results over time despite positive results with the earlier, small-headed implant design (the so-called second MoM generation) [4]. Retrieval analysis helps to improve the judgment for revision surgery of current MoM patients. Further, it is hoped that the lessons learned are applicable to designs with other bearing combinations as well.

Recovered and analyzed correctly, retrievals can provide clues about the specific materials used, their manufacturing process, the host response, the occurring wear

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modes of the device together with the underlying wear mechanisms, and the presence or absence of corrosion.

In this chapter, the authors will give an overview on the outcome of MoM hip retrieval analysis and the vital knowledge obtained so far. Although device fracture is known to occur in some rare cases due to overload or poor metallurgy, one of the main causes for clinical failure is related to wear and corrosion by initiating adverse local tissue reactions [5]. Therefore, focus is given to damage caused by wear and corrosion. First, the authors will demonstrate how insight into the retrieved material itself (i.e., cobalt-chromium-molybdenum (CoCrMo) alloy) can be obtained through appropriate tools. This is followed by an introduction to wear analysis, paying particular attention to the specifics of CoCrMo. Retrieval analysis ideally follows the principle of "from macro to nano". For this approach, global damage features should be evaluated first by photo documentation and macroscopic (magnifying glass) analysis techniques followed by microscopic (light microscope, white light interferometry) and nanoscopic (electron microscopy, atom force microscopy) methods. Since not only the emission of wear particles but also the release of ions is of concern, corrosion will be discussed as well. Emphasis is given to the use of modularity in femoral components, in particular the head–neck taper junction. The chapter closes with conclusions and recommendations on the handling of retrieved implants.

Type and Quality of Alloy

Every retrieval analysis should begin with the identification of the exact type of device (model, manufacturer, lot number) that is being evaluated. Also, all clinical information is of relevance and should be documented. Such information includes patient age, gender, body mass index, original diagnosis, clinical assessment scores, duration of implantation, and reason for revision. Further, detailed information about the alloy composition is warranted, which can be attained through energy dispersive X-ray analysis (EDX), if unknown. MoM hip prostheses are usually made from CoCrMo alloy, typically consisting of cobalt as the base, 26–30 % chromium and 5–7 % molybdenum, along with 0.05–0.4 % carbon and < 0.05 % nickel [6, 7]. CoCrMo alloy has been known for its wear and corrosion properties for a long time and has been used in the automotive and tooling industry first before it made its appearance in the dental field as Vitallium in the 1930s [8] and later in orthopedics in the 1940s [9]. CoCrMo is a highly abrasion-resistant material, in part due to its hard phases, which are distributed throughout the CoCr matrix and along the grain boundaries. The high corrosion resistance is provided by the high amount of chromium and molybdenum within the alloy. Chromium enables passivation by the formation of a protective chromium oxide film on the surface, which typically has a thickness of a few nanometers [10, 11]. During implant articulation, this film changes its composition and becomes a metallo-organic compound consisting of wear debris, proteinaceous and graphitic material [12, 13] as will be outlined in more detail further.

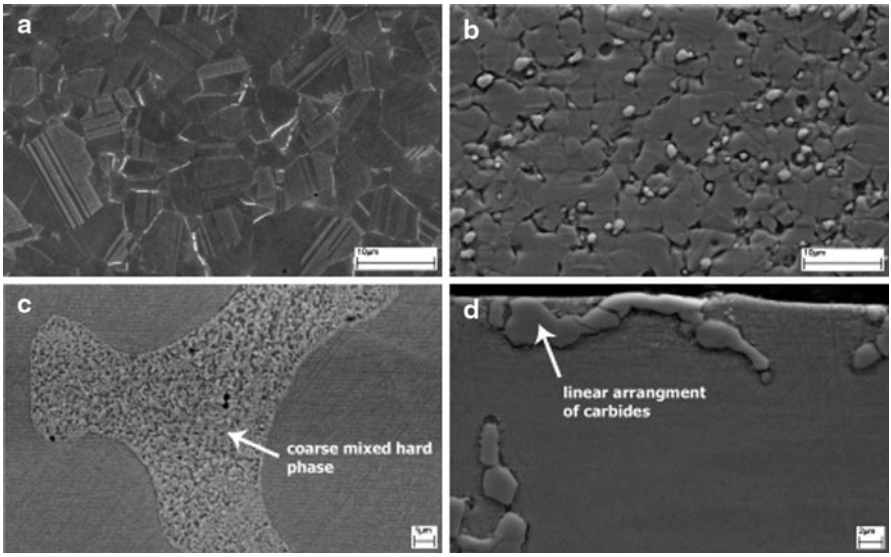

Fig. 11.1 SEM images of different CoCrMo alloy microstructures and hard phases. **a** Low-carbon wrought alloy, fine grain size, high twin density, minimal amount of hard phases. **b** High-carbon wrought alloy, fine grain size, evenly distributed fine and compact carbides. **c** As-cast alloy with coarse mixed hard phases. **d** HIPed cast alloy, linear arrangement of carbides

Two basic types of alloys have been used for orthopedic bearing applications: cast and wrought CoCrMo alloy. When a component is directly casted to its final shape, one speaks of cast alloy. After solidification of the alloy the component undergoes only surface finishing and in some cases heat treatment [14, 15]. Wrought alloy is first manufactured to bar stock. Its microstructure can be refined by forging as well as other methods, for example, vacuum induction melting [16]. It is usually more homogenous than cast alloy and has a smaller grain size. The chemical composition and mechanical properties of cast and wrought alloy are specified in ASTM F75 and ASTM F1537, respectively [6, 7]. These standards, however, do not set precise guidelines for the alloy microstructure. Hence, the quality between standardized materials fluctuates tremendously, the grain size in particular, as well as size and distribution of hard phases are not sufficiently standardized [17]. For retrieval analysis, knowledge of the microstructure is important since it is often not only directly related to material properties (e.g., hardness, yield strength) but also wear features on the surface. For example, since wrought alloy typically has a smaller grain size than cast alloy, it exhibits higher strength. Since grain size is inversely related to hardness, and metal hardness correlates directly with abrasive wear resistance, wrought CoCrMo alloys perform better under sliding conditions [16]. In order to visualize the microstructure of retrieved components, standard metallographic methods may be applied. A small section of the device has to be cut off, grinded, polished, and etched. Depending on the etchant, the hard phases, grain boundaries, or even both can be stained and visualized by light microscopy and/or scanning electron microscopy (SEM). In Fig. 11.1, a selection of observed CoCrMo alloy microstructures and hard phases is shown.

The amount and nature of hard phases depend on the amount of carbon within the alloy as well as the applied heat treatment [15, 17, 18]. As previously mentioned, the occurrence of the desired hard phases, so-called carbides (because of their chemical compound structure consisting of carbon and chromium and/or molybdenum), is directly related to the carbon content of the alloy [19]. However, a recent study has shown that not only carbides but also brittle intermetallic phases occur which can damage the bearing surfaces once they leave the metal matrix [17] (Fig. 11.1). In newer generation MoM hip joint implants, high-carbon (0.2–0.4 %) alloy is used more or less exclusively, which yields a higher amount of carbides [16]. Cast alloy implants may or may not undergo further heat treatment depending on the manufacturer. The heat treatment can have a big impact on the microstructure, especially its hard phases. The most common conditions for cast alloys are as-cast (no heat treatment), hot isostatically pressed (HIP), or double heat treatment (solution annealing and HIP). The total hard phase volume fraction can vary between 0.5 and 7 % depending on the heat treatment and solidification sequence. Based on prior studies, there is no consensus as to which type of heat treatment is preferable [15, 16, 20–22].

Wear

It appears that implant wear is directly related to the occurrence of adverse local tissue reaction and subsequent implant failure [23, 24]. Excessive wear can be design specific or to other factors, for example, malalignment [25, 26]. Thus, the focus of retrieval analysis is to understand how the components were worn, which type of wear debris was generated and how it affected the surrounding tissue. Wear analysis of orthopedic implants falls into the research field of tribology, which comprises scientific and technical aspects of friction, wear, and lubrication [27]. A hip joint is regarded as a tribological system which consists of four principal elements: body (femoral head), counter body (acetabular cup), interfacial fluid (synovial fluid), and the environment (regulated by the human body) [28, 29]. The interaction of these elements, depending on applied load, motion, and surrounding conditions (e.g. lubricant properties, local pH, temperature, etc.), results in material loss (wear debris) as well as heat and sometimes sound (squeaking).

Wear Modes and Mechanisms

In tribology research, the wear mode describes the general mechanical conditions under which a tribological system is operating. It is important to identify the wear mode and its underlying wear mechanisms during retrieval analysis. Currently, four major wear mechanisms are known, namely, adhesion, abrasion, surface fatigue, and tribochemical wear (Fig. 11.2). Knowledge of the acting wear mode and mechanisms is crucial as it provides information for appropriate wear countermeasures [28, 29].

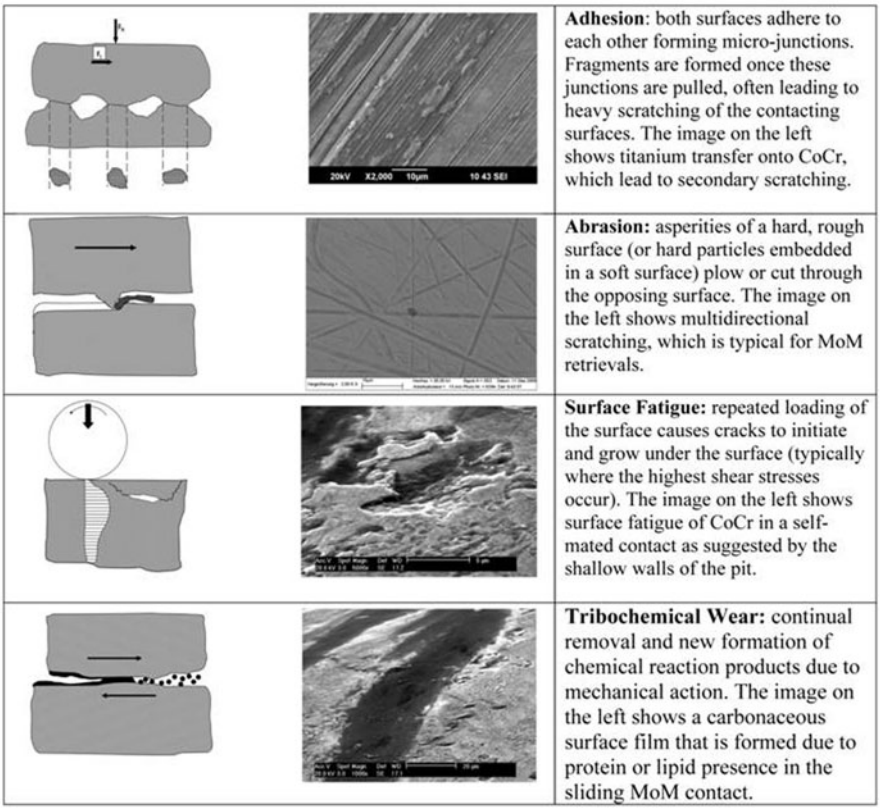

Fig. 11.2 Pictographs describing the four major wear mechanisms and examples of their appearance on cobalt-chromium alloy surfaces. It should be noted that wear mechanisms rarely occur in isolation but often take place together affecting each other

In order to determine the wear mode, the macroscopic structure of the system and the kinematic interaction of its elements have to be analyzed. Two fundamentally different wear modes are sliding and rolling wear with different subsequent wear mechanisms [28]. The knee joint, for example, exhibits a combination of rolling and sliding wear, whereas at the hip joint, only sliding wear occurs. During sliding, depending on activity, the relative motion between head and cup can be either unidirectional or reciprocating. However, complex motion causes motion trajectories on the surface to cross each other in a way that the direction of motion on single contact spots changes frequently. This wear mode is called specifically multidirectional sliding wear and is known to influence the wear rate, especially in the case of metal-on-polyethylene bearings due to the effect of orientation-softening on the polyethylene surface [30]. In summary, the wear mode of a hip joint under well-functioning conditions can be characterized as multidirectional sliding wear.

As shown in several studies, an increase in wear is often triggered by malpositioning of the hip joint resulting in edge loading or other adverse, non-intended

contact conditions (e.g., impingement) and subsequently accelerated wear [25, 31]. Therefore, the definition of wear modes for hip replacements was expanded and additional, non-intended wear contact conditions were included [32]. According to McKellop [32], there are four distinct wear modes that should be considered. Wear mode 1 describes wear conditions as intended for the implant design. Wear mode 2 is defined as contact between a bearing and a nonbearing surface. For example, this can be (a) edge loading, where the head articulates against the rim of the cup; (b) microseparation between head and cup leading to cyclic hard impact; and (c) impingement wear, which describes the contact between femoral stem and rim of the cup [25, 32, 33]. All three conditions have been observed frequently on retrieved specimens and proved particularly problematic for MoM [31, 34, 35]. In comparison to polyethylene, these "adverse wear conditions" lead to highly accelerated particle and ion release in MoM bearings often followed by catastrophic clinical failure. In hindsight, it would have been prudent to more thoroughly investigate these non-intended wear conditions for MoM hips preclinically. Wear mode 3 occurs when hard particles enter the tribological interface, and contact is established on this interfacial material. This wear mode is therefore also called "3-body wear." There is evidence from retrieval analysis [17] showing that the aforementioned brittle hard phase, break loose and enter the bearing surface. This leads to extensive scratching (and hence an increase in surface roughness) with breakdown of any occurring lubricant film and thus to increased wear. Finally, wear mode 4 has been defined as contact between two nonbearing surfaces, as for example backside wear between the metal shell and the liner of the bearing, and wear due to modular taper junctions. In particular, the latter turned out to be a tremendous problem for MoM total hip replacement with large head sizes leading to recalls of several devices on the market [36, 37]. Later in this chapter, we devote a separate section to taper wear.

Each wear mode is characterized by a specific combination of wear mechanisms, which may act in isolation or together. As mentioned earlier, knowledge of the wear mechanism provides the key for appropriate wear countermeasures. The four major wear mechanisms adhesion, abrasion, surface fatigue, and tribochemical wear have been described in detail elsewhere [28]. Briefly, adhesion leads to the formation of local junctions between the contacting surfaces, and thus has to be avoided for MoM systems to prevent catastrophic damage up to complete seizure. In well-lubricated MoM bearings, with large enough clearance, adhesion is not a problem [38]. However, the combination of a tight clearance, high contact pressure, and the absence of lubricant could provide the necessary condition for microwelding. Abrasion is characterized by hard asperities/particles cutting and plowing through softer surface. It is easily observed by the presence of scratches and grooves on the surface and occurs frequently. Its direct contribution to the overall wear loss is relatively low; however, it may have indirect effects, as for example the loss of the lubricant film, which is troublesome. Surface fatigue occurs due to repeated loading and unloading of the contacting bodies inducing small cracks underneath the surface and represents an important mechanism of wear for MoM joints [38, 39]. The cracks eventually grow and eject material fragments leading to pits or delamination. There were several reports of "micropitting" on the surfaces of MoM bearings, which could be linked to

surface fatigue. Since these cracks occur in the upper zone of the surface, the volume loss due to this mechanism is relatively low and leads to mild wear. Tribochemical wear results from the continuous removal and new formation of chemical reaction products. Since this mechanism occurs in a corrosive environment in the presence of proteins, the kinetics of this process become very complex for MoM joints. The importance of tribocorrosion for MoM joints has been underestimated for a long time, and only recently has become a major field of study [10, 40].

Wear Volume and Location

Metal ions and wear particles have been described as the trigger of adverse local tissue reactions [41]. At revision surgery, the periprosthetic tissue of MoM devices often exhibits a dark color indicating the massive invasion of metal particles and/or ions, which has been defined as metalosis [42]. It is difficult (if not impossible) to measure the wear of MoM devices during follow-up using X-ray film (as it is done in the case of polyethylene). Available markers are Co and Cr blood ion levels. Threshold levels were recently set to 7 μg/L by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK and others [43, 44]. But how much material was really removed from the surface over the entire lifetime of the implant? Metrology methods (e.g., measurements using coordinate or roundness-measuring machines) allow the precise determination of the total material loss from retrieved components [26, 31]. If the in situ time is known, a linear wear rate can be determined. For MoM bearings, the wear rate should not exceed 1–5 microns/year (approximately 0.5–1 mm^3). A higher wear rate will most likely lead to adverse tissue reactions [21, 42]. The wear rate of metal hip replacements does not follow a strictly linear evolution but wear occurs in two phases, namely, running-in and steady state [45]. As shown by simulator studies, the running-in phase exhibits a significantly higher wear rate than the steady state phase (Fig. 11.3) [45]. On average, it is estimated that the steady state phase is reached after 1 year. High wear volumes are troublesome as it has been shown that they directly correlate with high blood ion levels [23, 24] and the occurrence of adverse local tissue reactions [42, 46].

Several studies demonstrated that malpositioning of MoM hip joints triggers an increase in wear rate and thus initiates failure [25, 31, 34, 37]. For this discussion, malpositioning is defined as placing the cup out of a manufacturer's defined safety window of inclination and anteversion angles. The result can be a shift of the wear mode from 1 to 2. Retrieval analysis helps to accurately visualize wear scars generated due to edge loading, microseparation, or other possible adverse contact conditions [26, 47]. The metrology data can be used to generate a wear map which shows the projection of local penetration on the articulating surfaces of head and cup as shown in Fig. 11.4. In case of well-functioning hips, the maximum penetration of the cup due to wear should be located within the primary articulating surface area and be concentrated in close proximity to the pole of the head and the superior area of the cup, but not reaching the edge [26]. The transition from a high-wear area to a

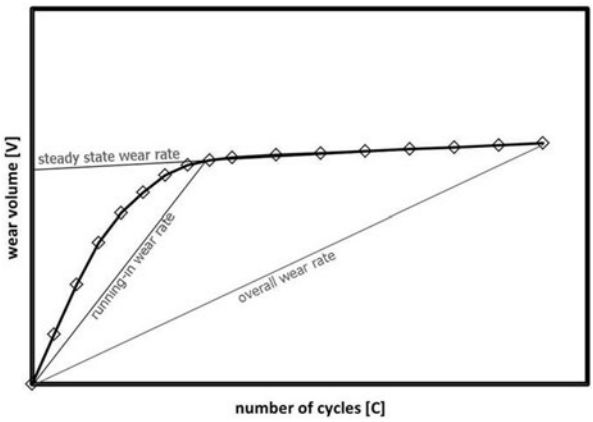

Fig. 11.3 Example of typical wear behavior in hip joints as derived from a hip simulator illustrating the difference between overall, running-in, and steady state wear rate

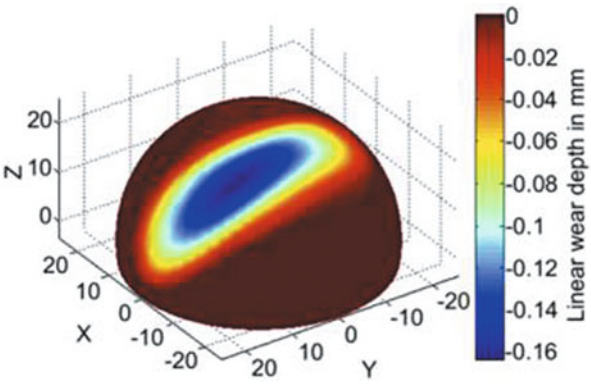

Fig. 11.4 Surface reconstruction of a femoral head based on metrology data, exhibits typical wear scar for edge loading or microseparation. (Reprinted from Langton et al. [47])

low-wear area should be smooth. During edge loading, the area of greatest wear is shifted to the edge of the cup [26]. The femoral head usually exhibits an oval wear scar, which can stretch from the trunnion up to the pole forming a stripe. Therefore, it is also referred to as stripe wear [33]. Adverse contact conditions are often displayed as clearly separated areas of damage. In the case of microseparation, the wear scar on the head exhibits numerous oriented scratches due to frequent contact with the edge of the cup as shown in Fig. 11.5.

Wear Features

Wear features or wear patterns describe the surface appearance within the wear scar. They are the direct result of the acting wear mechanism(s). Under well-functioning conditions, two wear features are most common in MoM joints: polishing and the formation of a tribofilm. Polishing can hardly be distinguished from the final surface finish process during manufacturing and is the result of fine wear particles ($\ll 1\ \mu m$)

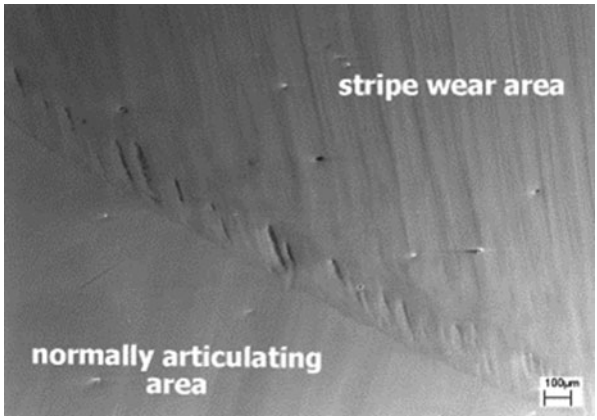

Fig. 11.5 Sharp transition zone between stripe wear area and normally articulating area on a femoral head. The stripe wear area exhibits numerous strongly oriented scratches and grooves

rolling between the articulating surfaces causing mild surface fatigue. The tribofilm forms due to combined interaction of the implant surface, fine wear particles, and protein from the synovial fluid (e.g., albumin, globulin). The resulting carbon-rich film covers parts of the articulating surface and serves as solid lubricant (Fig. 11.6). Further, it separates the two metal surfaces and thus inhibits adhesion which otherwise would increase the wear rate. On most retrievals, randomly oriented scratches can be observed as well (Fig. 11.7). Such scratches are the result of occasional abrasion due to 3-body wear. Hard abrasive particles are most likely to originate from the alloy itself due to detached hard phases. Depending on the type, size, and amount of hard phases in the alloy, the extent of occasional 3-body wear may differ. Although it is assumed that a large amount of hard phases reduces 3-body wear due to increased resistance to abrasion [14], evidence suggests that detachment of hard phases from the surface may introduce 3-body wear in the first place [17] (Fig. 11.7).

Under adverse contact conditions (wear mode 2 and 3), wear features may change drastically. For example, under edge loading or microseparation, wear is clearly more mechanically dominated and abrasion becomes the most dominant wear mechanism

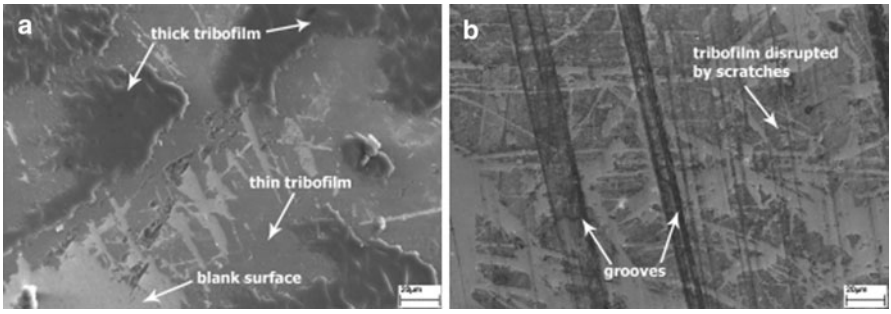

Fig. 11.6 Carbon-rich tribofilm on the articulating surface of a femoral head **a** under normally articulating conditions (wear mode 1) and **b** after edge loading/microseparation conditions (wear mode 2)

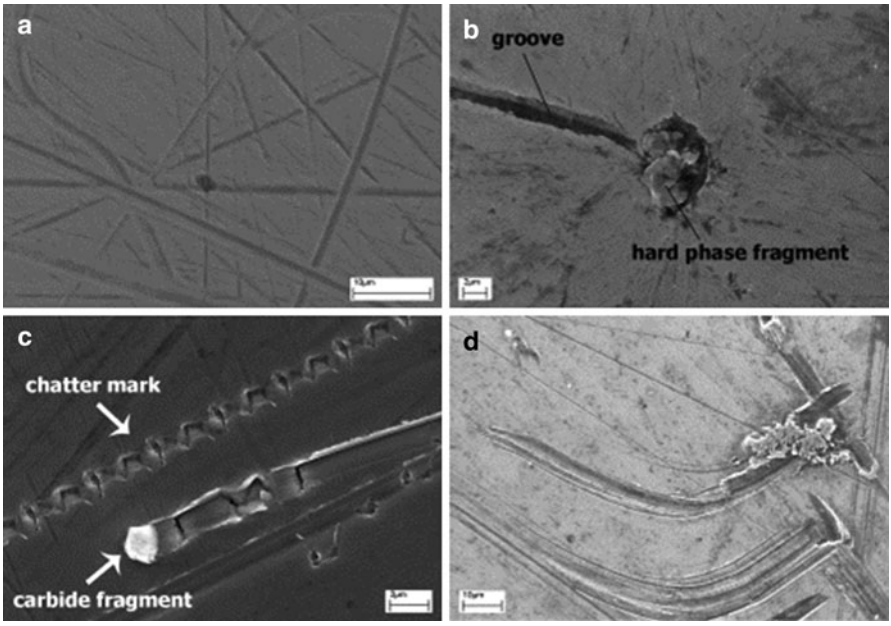

Fig. 11.7 SEM images of wear features caused by abrasion. **a** Randomly oriented scratches due to 3-body wear. **b** Groove caused by plowing hard phase fragment. **c** Chatter mark and grooves caused by carbide. **d** Grooves and scratches

(Figs. 11.5 and 11.7). In the affected areas, oriented scratches and deep (> 1 μm) grooves can be observed. Around the main wear area also, an increased amount of randomly oriented scratches can be found due to the wear particles generated in the edge loading/stripe wear areas, which are now introducing increased 3-body wear. A tribofilm may form as well in some areas, but it appears patchy and cannot unfold its beneficial influence on the implant wear behavior (Fig. 11.6). Several other wear features have been reported for adverse contact conditions which can be characterized as subgroups of those reported here.

Wear of metal devices not only causes morphological alterations on the articulating surface but also has impact on the immediate subsurface microstructure. Such alterations occur within the first few micrometers underneath the surface. Retrieval analysis of a group of well-functioning MoM hip replacements has shown that CoCrMo alloys undergo distinctive changes in the primary articulating zone [48]. Here within the first 400 nm, a nanocrystalline subsurface zone forms that gradually increases in grain size throughout depth. Also, the lattice structure of the alloy changes from the common face-centered cubic (fcc) lattice to the hexagonal close-packed (hcp) lattice. The grain size in this zone lies somewhere between 30 and 80 nm, and thus is significantly smaller than the bulk alloy [48]. Moreover, in some areas the nanocrystalline metallic surface shows incorporation of carbonaceous material, which originates from the earlier described tribofilm. Overall, the resulting metallo-organic composite material has beneficial influence on the wear

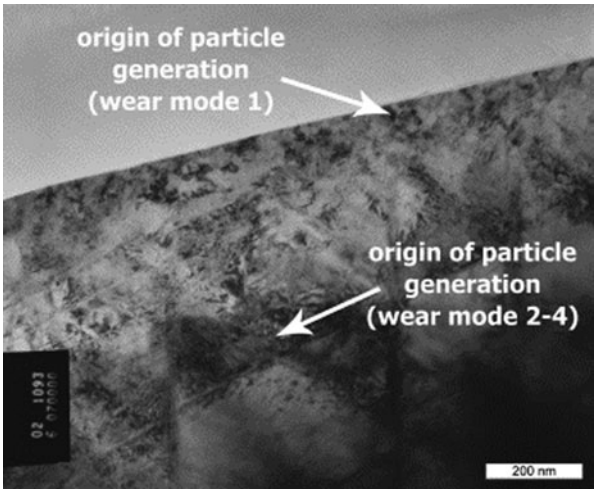

Fig. 11.8 TEM cross-section image of a femoral head articulating subsurface zone. On *top* a thin nanocrystalline layer can be seen. Under wear mode 1, nanoparticles are generated only within this area. Under adverse contact conditions, particles detach underneath that layer resulting in larger particles

and corrosion behavior of the bearing [13, 49]. If edge loading or microseparation occurs, the subsurface microstructure exhibits a slight but distinctive difference: The nanocrystalline subsurface zone is very thin (100 nm) and displays a sharp boundary with no transient changes to the underlying bulk microstructure.

The in situ alteration of the CoCrMo alloy subsurface microstructure is an important component in the understanding of MoM hip wear. However, its analysis requires sophisticated techniques, most importantly the use of a transmission electron microscope (TEM), which is not always available. Besides, sample preparation is time consuming and requires skilled personnel. Implant surface samples need to be locally thinned to a thickness of < 100 nm. This can be achieved with dimple grinding and ion milling [39], or with a focused ion beam (FIB) device paying close attention not to alter the existing microstructure. Once a sample has been prepared, an electron beam can be transmitted through the sample in the TEM. Many TEMs are further equipped with EDX or EELS (electron energy loss spectroscopy) which provide additional information of the local chemical composition and structure. Sample preparation and analysis have to be handled with great care to avoid the introduction of artifacts that could lead to wrong interpretation. Overall, such analysis gives valuable information, but it is time consuming and destructive and therefore should be applied to the most representative components available.

Wear Particles and Adverse Tissue Response

In well-functioning metal hips (wear mode 1), during steady state, it can be expected that the origin of particle detachment is strictly limited to the nanocrystalline zone (Fig. 11.8) [39, 49]. Thus, the particle size correlates with the immediate subsurface grain size. This can be observed on retrievals since polishing as a wear feature

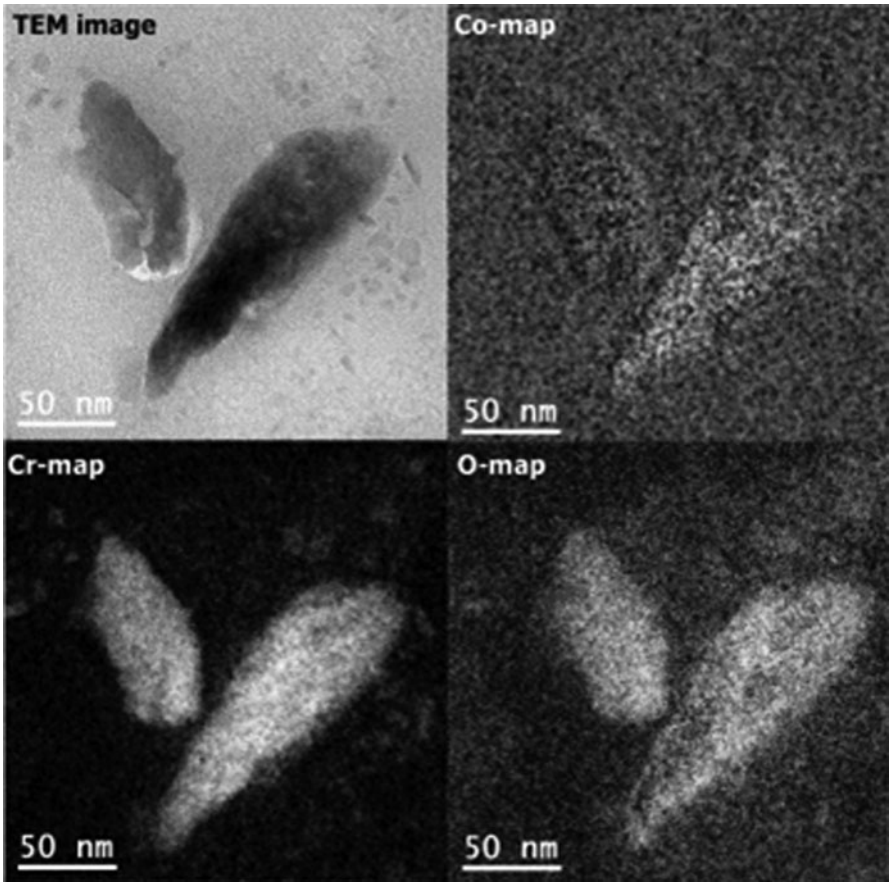

Fig. 11.9 TEM image and elemental maps (measured by EFTEM) of wear particles generated in a hip simulator. It can be seen that wear particles consist mainly of Cr and O, indicating the presence of chromium oxide. Remains of cobalt occur only locally in particles with a size > 50 nm. (Modified from Pourzal et al. [52])

indicates that most particles are very small, so they act more like a polishing paste rather than abrasive particles. Also, particles observed within the tribofilm were in the same size range [49]. This was confirmed by earlier studies of wear particles which were isolated from hip simulator wear-testing fluid (bovine serum) [50, 51]. It showed that such particles are in a size range of 30 to 80 nm. In general, particles of that size (< 100 nm) are considered nanoparticles and known to be highly reactive, especially in a biological environment. Indeed, energy-filtered TEM (EFTEM) analysis of such wear particles showed that the majority of wear particles consists of chromium oxide with almost no remains of cobalt (Fig. 11.9) [52]. Most of these particles are small (< 40 nm) and only a few, larger particles (> 60 nm) still contain cobalt. Thus, it must be assumed that these particles are highly reactive (pyrophoric) resulting in fast formation of small chromium oxide particles and cobalt ions. Under adverse contact conditions, as for example edge loading and microseparation, abrasion takes

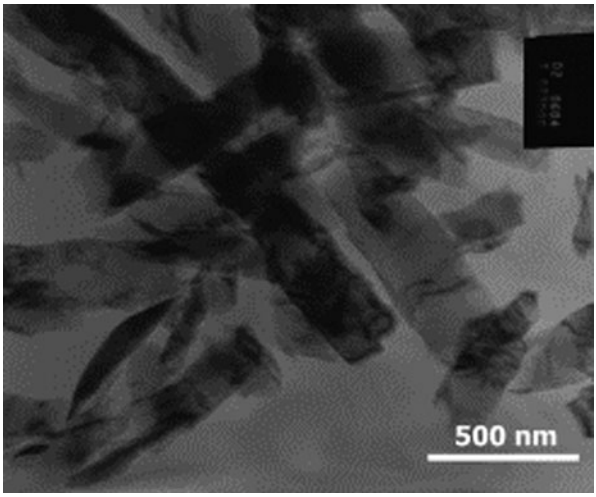

Fig. 11.10 TEM image of wear particles generated under adverse contact conditions. The particle size reaches from 200 to 800 nm. (Modified from Pourzal et al. [52])

stage as most dominant wear mechanism resulting in excessive scratching due to 3-body wear (Fig. 11.7). Under such conditions, as illustrated in Fig. 11.8, particles are no longer generated within the nanocrystalline zone but well below it. This leads to larger particle sizes up to 1 μm (Fig. 11.10). Such wear particles are chemically significantly more stable than nanoparticles. It was shown by Pourzal et al. [52] that the crystal structure of these particles is the same as that of the alloy subsurface zone. Just like the bulk alloy, the particle is protected by a chromium oxide passive film, which inhibits corrosion and thus chemical alteration.

Excessive generation of wear particles and release of metal ions from MoM bearings can induce adverse local reactions in the periprosthetic tissues [53]. The type and occurrence of local adverse tissue reactions differ depending on the nature of the wear particles, especially with respect to their size [54]. In vitro studies have suggested which particles or ion species might be primarily responsible for tissue necrosis [55–59]. High concentrations of Co^{2+} are toxic to macrophages and other cells. Cr^{3+} as well as chromium oxide may be comparably less harmful [57, 59]. This can manifest as a macrophage foreign body response to metallic particles or, in some patients, as a lymphocyte-dominated inflammatory response [60], leading to widespread necrosis of soft tissues, osteolysis, and failure of an arthroplasty. One or the other reaction may be present, or in some cases, both the foreign-body macrophage and the lymphocyte-dominated inflammation can be observed in the same specimen. A detailed description of the histopathology is presented in this volume in Chap. 9 by Bauer.

Corrosion

Corrosion is the gradual destruction of a material due to chemical interaction with its environment. Unlike wear, the material loss occurs mainly by ion release instead of particle formation. CoCrMo alloy is considered a corrosion-resistant alloy mainly

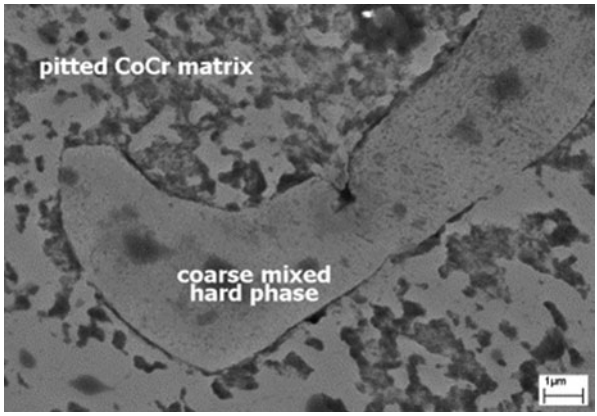

Fig. 11.11 Excessive pitting corrosion on the articulating surface of an as-cast alloy hip resurfacing femoral head. Pitting mainly occurred locally in the direct proximity of coarse mixed hard phases

due to the formation of a continuous passive film that consists primarily of chromium oxide (Cr_2O_3). It has to be stated that corrosion can never be separated from metal wear. Wear can usually cause local disruption of the passive film resulting in corrosion of the surface. Alloys like CoCrMo are able to rebuild the passive film rather quickly. However, there is always a contribution of corrosion during the wear process. The study of the combined interaction of wear and corrosion is subject of the field of tribocorrosion [10, 40].

Bearing Surface

Under well-functioning conditions of the implant, corrosion plays only a minor role on articulating surfaces and no specific damage pattern can be observed. However, in some rare cases, so-called pitting corrosion occurred leading to high blood ion levels and adverse tissue reactions [61]. This excessive type of corrosion is characterized by numerous pits, which can spread several micrometers. An example is shown in Fig. 11.11. The reason for the occurrence of pitting corrosion may be local galvanic elements that occur due to inconsistent metallurgy of the alloy or pairing of two different alloys between head and cup. Inconsistent metallurgy can be best observed by metallographic analysis as previously mentioned. The occurrence of excessive pitting corrosion is very rare on the articulating surface. A more prominent source of high ion release due to corrosion is the modular taper junction of total hip replacements.

Corrosion of Modular Junctions and Adverse Tissue Response

The investigator of retrieved implants should be aware that the bearing surface is not the only potential source of metallic particle generation and metal ion release in MoM total hip arthroplasty. For this reason, all surfaces of retrieved devices should

be thoroughly examined for evidence of wear and corrosion with particular attention to the mating surfaces of modular junctions. Marked corrosion has been reported at modular head–neck junctions [62] and at the junction between dual modular necks and femoral stems [63]. A lymphocyte-dominated adverse local tissue response similar to that seen with MoM bearings may occur when one or both components of a corroded modular junction are made of CoCr alloy.

The nature of corrosion, the identification of solid corrosion products, and the serum cobalt and urine chromium concentrations associated with modular head–neck junctions have been studied extensively in earlier generation devices with metal-on-polyethylene bearings using SEM, EDX, X-ray diffraction, EELS, and atomic absorption analysis [64–68]. Corrosion attack of modular CoCr components included preferential dissolution of cobalt, pitting, and intergranular corrosion [64]. Serum cobalt and urine chromium concentrations were significantly elevated in patients with moderately or severely corroded tapers [66]. At the corroded modular connections, solid corrosion products were found at two locations [67]. A thin, friable interfacial layer of highly crystalline mixed oxides and chlorides of chromium and molybdenum was present within the crevice formed by the mated head and neck components. Thicker deposits identified as amorphous chromium phosphate were present around the opening of the crevice. Migration of brittle chromium phosphate corrosion products to the bearing surface was demonstrated throughout the periprosthetic tissues [65] and to para-aortic lymph nodes [69].

Contemporary modular head–neck junctions of improved design and the more recently introduced dual modular CoCr necks demonstrate same types of corrosion and corrosion products (Fig. 11.12) as earlier modular head–neck designs described previously [62, 63]. Both foreign-body macrophage and lymphocyte-dominated inflammation can be observed in the periprosthetic tissues from contemporary modular junctions (Fig. 11.13). Corrosion of these devices may not be immediately apparent on gross examination of the retrieved component or when using reflected light microscopy, even under moderate magnification. A slight dulling of the surface, a matted surface appearance, or a bright surface with the presence of corrosion products may be the only indication of corrosion. In such specimens, examination with SEM can reveal extensive pitting corrosion (Fig. 11.14) or intergranular corrosion of modular junctions. Modular head–neck and CoCr dual modular necks can be sources of metallic particle generation and metal ion release in addition to the bearing surface in MoM total hip devices and should be carefully examined when assessing retrieved components and relating their retrieved condition to the clinical performance of an arthroplasty.

Summary and Recommendations on Retrievals Handling

In this chapter, we have shown that retrieval analysis can provide helpful information on the failure mechanism of specific implants. Macroscopic and microscopic techniques help to identify the wear mode(s) under which the implant had operated

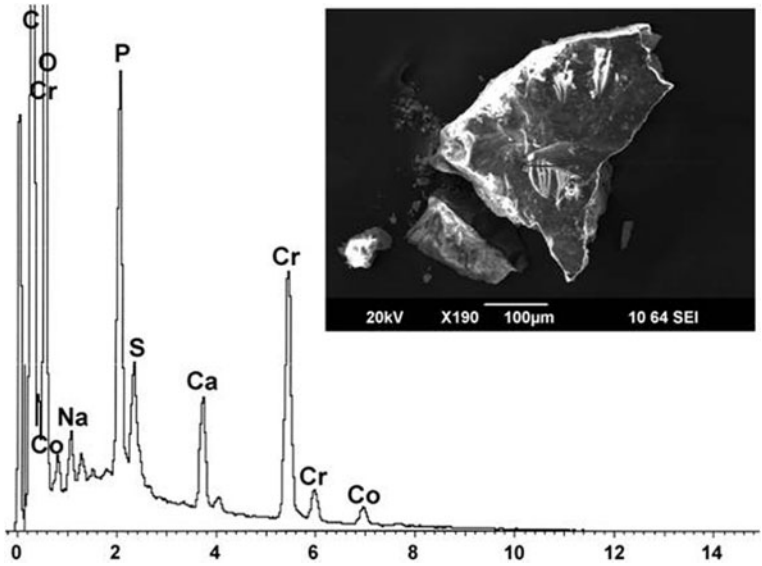

Fig. 11.12 Energy dispersive X-ray analysis spectrum of an approximately 350 µm particle (*inset*) from a contemporary head–neck junction with intergranular corrosion is high in chromium, phosphorous, and oxygen with a trace of cobalt and is typical of chromium phosphate corrosion product. The device was removed after 83 months for infection

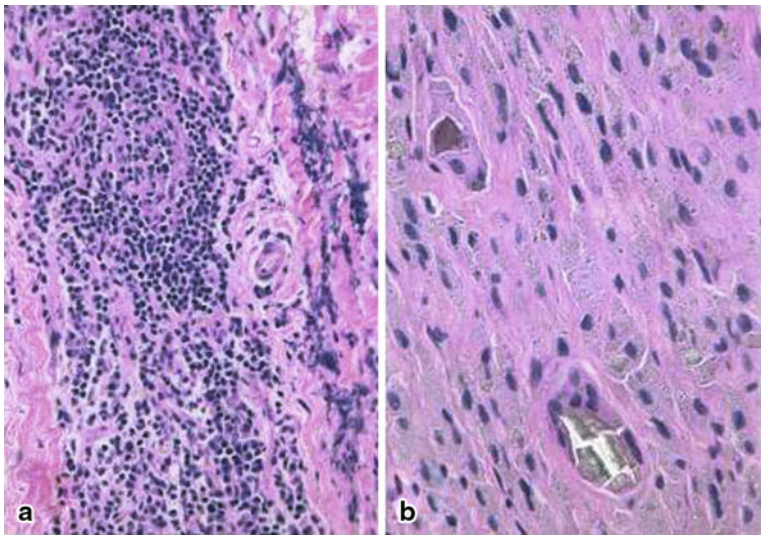

Fig. 11.13 **a** Lymphocyte-dominated inflammation in joint pseudocapsule surrounding contemporary CoCr/CoCr head–neck junction with intergranular corrosion (H & E, × 400). **b** Histiocytes and multinucleated giant cells laden with minute particles of chromium phosphate corrosion product adjacent to a contemporary CoCr/CoCr head–neck junction with intergranular corrosion (H & E, × 600)

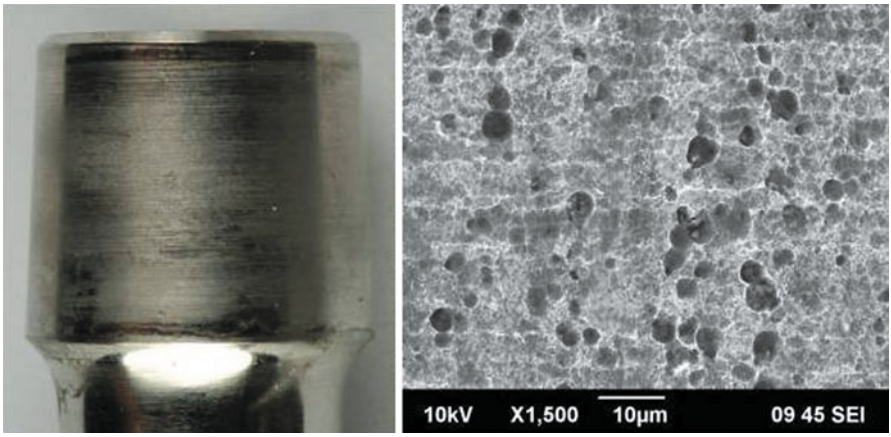

Fig. 11.14 Severe pitting and etching was observed on a contemporary CoCr neck taper mated with a ceramic head (*left*, gross appearance; *right*, scanning electron micrograph). The device was removed for lymphocyte-dominated local adverse tissue response 16 months following primary implantation

and determine the active wear mechanisms from the resulting wear features. Knowledge of the microscopic wear features enables the investigator to estimate the size of wear particles transported to the periprosthetic tissue and qualitatively estimate the amount of wear debris. This knowledge helps to better understand the biological response and histological findings and possibly avoid failures in the future. Retrieval analysis of well-functioning implants clearly demonstrated that MoM articulations can work satisfactorily. This knowledge should build the foundation for potential design changes.

It is important to treat the available retrievals with great care to avoid secondary damage during or after retrieval. Therefore, we want to encourage operating surgeons to support retrieval analysis and close this chapter with a few recommendations on retrieval handling. First of all, any damage to the articulating surface should be kept to a minimum if the course of the surgery allows it. It is recommended to place marks on nonarticulating parts of head and cup which determine the orientation of the components in vivo. Such marks will make the interpretation of wear scares (e.g., stripe wear) and wear features (e.g., oriented scratches) easier. Further, it has been shown that tribochemical reactions can play an important role for the longevity of MoM hip replacements. Therefore, it is of great importance not to perform any form of intensive cleaning directly after implant removal. Mechanical cleaning and the use of detergents should be avoided. Ideally, the retrieval is rinsed in distilled water and stored in formalin. Thus, tribofilms and other deposits (e.g., chromium phosphates), which may carry important information regarding the failure mechanism, will not be lost. After proper analysis and documentation of such films, they may have to be removed to analyze underlying morphological wear features on the articulating or taper junction surfaces.

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Future Directions

"The past as prologue" is an apt descriptor of where the future utilization of metal-on-metal (MoM) articulations and their attending tapered connections may lead as solutions for the treatment of degenerative hip arthritis. Literature citation, news reports, conflicting registry data, product recalls, and litigation involving contemporary MoM articulating total hip and surface replacement arthroplasty designs have played a draconian role in the curtailment of their clinical usage. Despite the negativity and rising clinical concerns of these reports, there are also reports in the peer-reviewed literature citing short- to intermediate-term successful outcome. Their total abandonment would render obsolete the unanswered questions that seek to explain observed negative phenomena leading to their revision. This book presents a series of contemporary insights into clinical, biological, and biomechanical questions that need to be addressed by established scientists and clinicians whose end purpose is to assure satisfactory outcome in the patients they serve.

Relief of pain and restoration of function is the sine qua non of hip reconstructive surgery; however, long-term successful outcome depends on in vivo device durability. Metal-on-metal articulations have been introduced as a long-term hard-on-hard bearing solution proffered with younger and active patients. While contemporary patient populations have been broadly defined for MoM articulations, the outcome studies included are suggestive of further refinement of patient selection criteria. Regulatory agencies and professional societies have published guidelines for the monitoring of patients with these articulations based on short-term adverse events. Patients presenting with pain, effusions, motion limitations, and elevated ion levels need careful and sequential clinical monitoring along with consecutive radiographic and perhaps, ultrasound visualization. The trigger point of when to intervene is not accurately defined. However, recent publications have suggested acceptable upper level serum blood ion levels for both unilateral and bilateral surface replacements as 4.6 and 7.4 μg/L for chromium and 4.0 and 5.0 μg/L for cobalt, respectively [1]. This blood ion level guide coupled with directional increases or decreases in these levels measured sequentially in a given patient, provides a trend indicator which must be compared to pathological change. More refined quantitative appreciation of histological and radiographic changes will further contribute to determining clinical intervention points. Currently, the cross-sectional imaging provided by metal artifact reduction sequence magnetic resonance imaging (MARS-MRI) scans delineates periprosthetic tissue changes and are evolving as a diagnostic tool. Adverse

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local tissue reactions (ALTR) inclusive of pseudotumors, osteolysis, and perivascular lymphatic infiltration are among these observations. A continuing question as to whether a preferred patient for MoM articulations can be a priori identified rests on more refined prescreening protocols. These must include standard patient evaluations with additional tests to identify metal sensitivity. Standard patch testing has been employed and there is a need for further test development perhaps based on reported lymphocyte proliferation response measurements that have been associated with MoM devices. While adverse tissue pathology has been recognized surrounding MoM hip implant systems in short- and intermediate-term reports, little is known beyond speculation of any potential long-term systemic consequences. The influences of metal ions and particulate to more distant tissues and body organs require the tincture of time in vivo. Thus, continued clinical monitoring, particularly of well-performing MoM systems, is required.

A common criticism of laboratory evaluation is that there is more often than not a disconnect between wear and structural performance predicted in the laboratory and that realized from in vivo retrievals. One must recognize that clinical outcomes are seen to be dependent not only on material and design selection but inclusive of patient factors and surgical proficiency. Tissue interruption and repair along with component selection and placement most assuredly contribute to outcome particularly when hard-on-hard articulating bearings are utilized. Edge loading recognized in clinical retrievals is not measured in standardized testing protocols. It is suggestive of component malalignment, which clinically is manifest through inclination and version. In vivo hip usage is inclusive of significant stop-start motion activities where functional loading varies dramatically and impacts the lubrication of MoM articulations. Currently, standard hip simulation laboratory testing does not take this into account which in turn negatively influences material damage and debris generation. These variabilities suggest directions which can bring laboratory testing more in line with in vivo observations derived from retrievals. A value of retrievals is then seen as assisting the continuous refinement of testing standards developed by both the American Society for Testing and Materials (ASTM) and the International Organization for Standardization (ISO).

The evolving use of component modularity through taper connections in femoral stem design has found application in both primary and revision hip procedures. The advantages of these systems include off-the-shelf flexibility for customizing proximal and distal canal filling, preservation of soft tissue structures, biomechanical restoration of offset, version and leg length, as well as accommodating difficult situations of femoral deformity and bone loss. Head-neck, mid-stem, and distal neck modular femoral systems are employed for a variety of patient skeletal pathology. In 2011, almost 460,000 primary and revision total hip arthroplasties were performed in the United States [2]. Of these, almost all involved head-neck modularity while 7–8 % involved both head-neck and mid-stem/distal neck modular femoral stem designs. When coupled with the soluble and particulate debris realized in MoM articulations, the significance of this added burden compounds the potential for ALTR in these systems.

Further, the most recent peer-reviewed literature cites the occurrence of tribocorrosive processes attributed to both fretting and crevice corrosion at these taper connections where at least one component contains cobalt. To date, the severity of

surface alteration has been qualitative and further efforts to quantitate the extent of these observations will prove explanatory in their significance. The influence of taper variability between both manufacturers and designs on the metal particulate and ion burden needs to be appreciated and then standardized. This will assist clinical utility during assembly and represents a fertile area for further laboratory investigation.

The embracement of MoM articulations with increased femoral head diameters have been employed as a remedy for dislocation but have also been associated with increased ionic burden and particular damage to head-neck tapers. The ying and yang of this practice needs to be carefully assessed—a further direction of laboratory testing and clinical reporting.

At the end of the day, the abandonment of MoM hip articulations is a bridge that should not be crossed. Their clinical utility indicates that there are still a significant number of unanswered questions whose appreciation might reduce the complications that have been reported to date while the majority still enjoy significant clinical benefit at mid-term reporting intervals. The chapters of this book elucidate what is known about many of the problems and point to future directions. Its content should be appreciated by scientists and engineers as well as regulatory agencies and professional bodies, not least withstanding the medical device manufacturing community; all of whom, in the end, have a vested interest in assuring good patient outcome.

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