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The Genotoxic Potential of Novel Materials Used in Modern Hip Replacements for Young Patients

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1. Introduction

Total hip replacement (THR), one of the most successful and cost effective surgical interventions introduced in the last 50 or so years in medicine and the second most common elective operation in the UK (Sheldon et al., 1996, Garellick et al., 1998), owes most of its success to the introduction of hard-on-soft arthroplasty by Charnley. Arthroplasty (from the Greek 'arthrosis' = 'joint' and '-plasty' = 'the making of') describes the surgical reconstruction or replacement of a malformed, degenerated or traumatised joint. THR is the treatment of choice for conditions that affect both the articular surfaces (i.e. acetabulum and femur) of the hip joint. Worldwide, approximately one million artificial hips are implanted annually (Smith & Learmonth, 1996). Problems with polyethylene (PE) wear debris from soft-on-hard articulations (causing an infiltration of macrophages, eventually leading to destruction of bone and soft tissue and initiating loosening of the implant) led to the development of hard-on-hard bearing combinations for artificial hips as the latter produce minimal wear and therefore implant failure is delayed.

Until recently, THRs have been reserved primarily for the elderly and with relatively short post-operative life expectancies there was no need for studies investigating the long term effects, since on average, prosthetic joints are relatively trouble-free for 10-15 years (Havelin et al., 2000). However, due to their success, a greater number of THRs are nowadays performed on increasingly younger, more active patients. In England a substantial proportion of THR patients (>12%, i.e. >10.000 individuals yearly) are below 60 (NHS, 2006). Bearing in mind that the use of artificial hips is more rigorous in younger patients and that life expectancy continues to increase, it is time that the question of possible adverse long term effects following implantation needs to be addressed. Most importantly, concerns for potential carcinogenicity of THRs is reasonable to be raised, since both soluble and particulate wear debris originating from the prostheses are biopersistant and are found systemically in the human body following the operation. In this chapter I discuss the proposed links between hip replacements and carcinogenesis to date by summarizing the relevant literature while presenting important background information regarding THRs, the generation of wear debris from hip prostheses, its biopersistence and the extent of its dissemination in the human body. This review is mainly focused on materials currently being used as bearing surfaces in artificial hips for younger patients.

2. Basic anatomy of the hip joint and indications for THR therapy

The hip joint is a multiaxial ball and socket synovial joint formed between the spherical head of the femur and the hollow cup-shaped acetabulum of the pelvis, which in turn forms at the union of 3 pelvic bones (the ileum, ischium and pubis). The depth of the acetabulum is increased by a fibro-cartilaginous rim (labrum) which grips the head of the femur and secures it in the joint. The head of the femur is attached to the femur by a thin neck region. Both joint surfaces are covered with a strong layer of articular hyaline cartilage, except for a small area in the head of the femur, the fovea or pit, from which an intracapsular ligament attaches directly to the acetabulum. A strong fibrous capsule is attached to the rim of the articular cartilage, enclosing the joint cavity. Thickened strands of this capsule form ligaments which support the joint. The whole joint cavity is lined by a membrane, the synovium, the cells of which secrete an oily fluid that lubricates the articulating surfaces and allows smooth movement of the ball within the socket. A network of blood vessels, lymph vessels and nerves is also present (Standring, 2004). The hip joint(s) form the primary connection between the lower limb(s) and the axial skeleton of the trunk and pelvis. Its primary function is to support the weight of the body in both static (e.g. standing) and dynamic (e.g. walking or running) postures. Its strong but loose fibrous capsule permits a large range of movement (second only to the shoulder).

Joint injuries are caused either by trauma or by gradual wear and tear due to aging and/or congenital predisposing factors. The hip joint frequently succumbs to degenerative and inflammatory diseases causing severe pain and stiffness, e.g. osteoarthritis and rheumatoid arthritis. Osteoarthritis, the most common form of chronic joint disease, results primarily from destruction and/or degeneration of the cartilage at the articular surfaces with age. In younger people, it may be the result of congenital dysplasia and/or dislocation, damage caused by fracture, previous inflammation etc. In fact, any situation which puts an unusual stress on the joint(s) can predispose to osteoarthritis (Flugsrud et al., 2002). Rheumatoid arthritis is an inflammatory disease of the connective tissue. It is more common in women and presents mainly between the ages of 25 and 55. Affected joints become swollen and tender due to inflammation of the synovium and escape of synovial fluid into the joint cavity. Although the disease often burns itself out in time, damaged joints continue to disintegrate, causing severe pain and stiffness. Hip joint fractures can occur at any age although they are more frequent in the elderly as they are closely associated with osteoporosis (i.e. a reduction in bone density due to decreased bone formation and/or increased bone resorption resulting in brittle bones). Osteoporosis' incidence increases with age and is most commonly seen in post-menopausal women but it can also begin very early in life. THR therapy aims to relieve pain and increases the patient's quality of life by comprehensively restoring the structure and function of the hip joint via complete replacement of the head of the femur and the lining of the joint socket on the pelvis with artificial materials (Smith & Learmonth, 1996, Garellick et al., 1998).

3. A brief history of THR and the modern artificial hips – Design & materials

The first recorded THR was performed in 1938 by Philip Wiles, using a total hip made entirely of stainless steel. The acetabular cup was fixed with two screws while the femoral component was secured by a bolt that passed through the neck of the femur (Amstutz &

Grigoris, 1996). The next major development was in 1951; the McKee-Farrar total hip was again made entirely of stainless steel however the stem was fixed using acrylic cement. In the late 1950s McKee and Farrar started operating more frequently with a Cobalt-based alloy (CoCrMo) as the principle bearing material. Various types of prostheses, including the McKee-Farrar, Ring, Stanmore and Muller designs, employed this bearing surface during the 1950s-1960s and it was not until the 1970s that metal-on-metal (MOM) articulation lost favour, mainly due to the successful design of the Charnley artificial hip which completely replaced all the other designs (Charnley, 1972). Accelerated corrosion because of improper selection of materials or faulty fabrication techniques (Jacobs et al., 1998a), and concerns about possible carcinogenesis (Heath et al., 1971), metal sensitivity and high infection rates eventually led to the abandonment of MOM articulation as soon as a better option was available (Amstutz & Grigoris, 1996).

While studying animal joint lubrication, Charnley realized that a cartilage substitute was necessary in order to allow artificial joints to function at the extreme low-friction level, as seen in nature. His innovative design consisted of a metal (hard) femoral component, a plastic (soft) acetabular component and bone cement. In 1958, he replaced an eroded arthritic socket with a thick walled Teflon cup, within which a small femoral head articulated, attached to an acrylic-fixed stem. The small (22.25mm) femoral head chosen was aiming for a decreased wear rate, however it had relatively poor stability (the larger the head of a replacement, the less likely it is to dislocate, but the more wear debris will be produced due to the increased articulating surface area) and failed quickly due to massive inflammation following PE wear production. In 1961, Charnley substituted Teflon with high molecular weight polyethylene (HMWPE) which is 500-1000 times more resistant to wear. In the 1970s, Boutin was the first to introduce alumina ceramic as a bearing surface in orthopaedics (Boutin, 1971). Ceramic-on-ceramic (COC) articulations produced minimal wear however early results were discouraging as these prostheses were very prone to fractures (Boutin et al., 1988). Thus, for over two decades, the Charnley Low Friction Arthroplasty design was the preferred system worldwide, far surpassing the other available options. Thousands of people were successfully relieved from their hip pain and the long-term results became more predictable. John Charnley was knighted for his efforts (Cornell & Ranawat, 1986a, b) and many similar designs (pioneered by Charnley) followed.

The current/modern artificial hips have three parts: (a) a rod or stem, which fits into the femur to provide stability and is usually made from metal (Ti- or CoCr-based alloys) while cement (poly-methyl-methacrylate) is sometimes used to fix it firmly in place; (b) a head or ball, which replaces the spherical head of the femur and is made of either hard, smooth metal (usually CoCr alloy) or ceramic (usually Al_2O_3) and (c) a shell or cup which replaces the faulty hip socket and allows bone to grow onto. Sometimes, a liner is used that locks into the shell and this in turn articulates with the ball. The cup can therefore be made of one or more materials, but the actual articulating surface that touches the ball is commonly made of CoCr-alloy, alumina or ultra high-molecular weight-polyethylene (UHMWPE). Each part is manufactured in various sizes in order to accommodate various body sizes and types. In some designs the stem and ball are one piece whilst other designs are modular, allowing additional customization for a better fit. In the U.S., all implant devices must be approved by the Food & Drugs Authority (FDA) and similar purpose governing bodies exist worldwide. In the U.K. approval must be given by the Medicines & Healthcare products

Regulatory Agency (MHRA) prior to clinical use of any THR implants. It is worth mentioning that an implant device may be approved in one country but not in another; e.g. COC total hips were widely used in Europe before they were made available in the U.S. (see www.mhra.gov.uk and www.fda.gov/Medical Devices).

In summary, finally, surface choices in modern THRs can be divided into hard-on-soft metal-on-polyethylene (MOP) or ceramic-on-polyethylene (COP) and hard-on-hard metal-on-metal (MOM) and ceramic-on-ceramic (COC) bearings.

4. Why do implanted artificial hips fail after all?

The ideal implant should stay in situ and function trouble-free indefinitely or at least for the whole of a patient's life. However, this is not an ideal world and revision operations following THRs are often needed after 10-15 years if not sooner (Jacobs et al., 1998b). So why do hip prostheses fail? Initial acute complications following THRs include improper placement, cement extrusion and dislocation. Although dislocation can also occur as a late complication, it is most common in the immediate postoperative period (Manaster, 1996). Late complications include failure of any of the components of the prosthesis, mechanical (aseptic) loosening, bone fracture, heterotopic ossification (bone formation), loosening following infection and osteolysis (also termed aggressive granulomatosis or debris synovitis) (Tigges et al., 1994). In approximately 20% of patients, the artificial hip becomes loose within 20 years after implantation (Doorn et al., 1996a, Doorn et al., 1996b) while aseptic loosening in THR accounts for approximately 75% of revision procedures (Amstutz et al., 1992). In an early study, Dobbs et al evaluated the survival of THR prostheses by measuring whether they were still in situ; MOM articulations were found to have lower survival rates than MOP ones (53% and 88% respectively); nonetheless, the predominant reason for failure/revision in both cases appeared to be loosening of the prostheses' components and authors blamed wear production for triggering osteolysis (Dobbs, 1980).

Initially termed 'cement disease' (Jones & Hungerford, 1987), osteolysis is now understood to be a biological response to particulate wear debris and may originate at several locations around a THR. Willert was among the first to hypothesize that aseptic loosening of THRs was caused by the local macrophage response to wear debris (Willert, 1977). Goldring et al subsequently described the synovial-like nature of the bone-implant interface in patients with loose THRs and showed that cells within the periprosthetic membrane had the capacity to produce large amounts of several 'bone resorbing factors' (Goldring et al., 1983). Although these initial reports were in cemented implants, similar processes have been identified recently in cementless implants (Ingham & Fisher, 2005). Interestingly, Havelin et al reported a significant increase in the annual number of revision operations in Norway mainly due to an increase of wear debris production and osteolysis without loosening. This finding presents a different situation to what was observed in earlier years, where most prostheses failed after aseptic loosening of their components (Havelin et al., 2000).

Osteolysis remains the main problem of THRs leading to revision surgery and a plethora of research studies have identified the generation of particulate wear debris from the articulating surfaces as a key factor. The amount of wear particles that are generated, their chemical composition, size and shape influence the induction of osteolysis (Meneghini et al., 2005). Micron and submicron wear particles (particularly of PE) have been identified as the

main cause of loosening of artificial hips, following osteolysis (Ingham & Fisher, 2000). The current hypothesis is that particulate wear debris released from the prostheses can invoke a biological response in the surrounding tissue. Adjacent to THRs, one can find synovial tissue, fibrous tissue, lymphocytes (occasionally) and foreign-body inflammatory cells (macrophages and giant cells) that are present roughly in proportion to the number of particles surrounding the prosthesis (Schmalzried & Callaghan, 1999). The macrophages appear to be the most relevant and important cells with respect to this biological reaction. As wear particles are released, macrophages ingest them in an attempt to clear them, become stimulated and release cytokines. The inflammatory response is marked by the accumulation of more macrophages at the implant site attracted via released cytokines (Ingham & Fisher, 2005). A chain of cytochemical events leads to the production of foreign body giant cells that release chemical mediators able to activate osteoclasts (Wang et al., 1997). During osteolysis, the activated osteoclasts resorb bone, with subsequent loss of integrity of the implant-bone interface, resulting in loosening of the implant and/or cyst formation and finally implant failure (Archibeck et al., 2000, Horowitz et al., 1993, Schmalzried et al., 1992, Wang et al., 1997). The number and the size of the wear particles appear to be the most important factors in determining the potential to elicit a biological response (Ingham & Fisher, 2000, 2005). Importantly, aseptic loosening and/or osteolysis requiring revision have also been reported for hard-on-hard, minimally wearing THRs using MOM and COC bearings (Harris, 1994, Yoon et al., 1998).

5. Modes of wear and the generation of different types of wear debris from hip prostheses

Wear is the removal of material that occurs as a result of the motion between two opposing surfaces, under load (Schmalzried & Callaghan, 1999). In THRs, these can be either the primary bearing surfaces of an articulating couple or secondary surfaces. The conditions under which the prosthesis was functioning when the wear occurred have been termed the wear modes. Mode 1 wear results from the motion of two primary bearing surfaces against each other, as intended; this is unavoidable. Mode 2 wear results from a primary bearing surface moving against a secondary surface that it was not intended to come in contact with (e.g. when a femoral head penetrates a modular PE liner and articulates with its metal backing). Mode 3 wear results from primary surfaces sliding against each other but with third body particles interposed (thus the contaminant particles directly abrade one or both of the primary surfaces which are in turn transiently or permanently roughened, leading to a higher mode 1 wear rate). Mode 4 wear results from rubbing together two secondary surfaces (e.g. a liner with a backing) and particulate debris generated this way can migrate to the primary bearing surfaces leading to third body wear.

There are four fundamental mechanisms through which wear debris can be generated: adhesion, abrasion, corrosion and fatigue. Adhesion involves the bonding of opposing surfaces when they are pressed together under load. Adhesive wear occurs when fragments usually from the weaker of two relatively smooth bearing surfaces break off and adhere to the opposing surface. A so-called transfer film may be formed, whose disruption and reformation may lead to extreme fluctuations in wear rate (McKellop et al., 1981). Abrasion is the mechanical process of surface grinding that takes place as a result of friction. Abrasive

wear occurs when asperities found on a relatively hard articulating surface cut and plough through a softer/smoother surface during the sliding motion, forming a series of grooves in the smoother surface. This results in the removal of material. The same process can also take place when other wear particles (e.g. cement), generated elsewhere, are caught between two bearing surfaces and exacerbate the wear process by scratching and scoring them; wear produced this way is called 'third body' (Sedel, 1992, Hamadouche et al., 2002). Corrosion is the deterioration of essential properties in a material due to reactions with its surroundings. There are several types of corrosive processes and corrosive wear can occur in the presence of a 'hostile' environment such as the human body. Regarding bearing surfaces, corrosion products can form a passivation layer which is continuously worn away by the sliding action of the articulating surfaces; thus corrosion can progress further generating both soluble and particulate wear debris. Fatigue arises when local stresses exceed the fatigue strength of a material, leading to its failure after a certain number of loading cycles and the release of wear debris from its surface and/or its fracture. In articulating surfaces, fatigue wear occurs during repeated sliding or rolling over the same area, in the presence of local surface features or bearing pair incongruities (i.e. unmatches). This produces accumulations of concentrated local cyclic stresses which exceed the fatigue limit of either material in the wear couple. Such concentrated cyclic surface loading leads to the formation of surface and subsurface cracks which can lead to surface break-up and the release of large fragments (Schmalzried & Callaghan, 1999).

Notably, deformation of any of the bearing surfaces is expected to result in increased (Mode 1) wear. Acetabular (component) deformation can be observed as a consequence of the press-fit technique, which is employed to fix equatorial over-sized implant cups in place without cement (Squire et al., 2006). As completely spherical cups have a considerable risk of being pushed out of the acetabulum due to the so called 'rebound effect' (combination of strong forces all around the cup), over-sizing cups around their equator allows a more reliable fixation by compression forces only. Nonetheless, cup deformation could adversely affect the bearing clearance (Springer et al., 2011) and thus the fluid film lubrication of MOM bearings, possibly leading to increased adhesive and/or abrasive wear. Deformation has also been implicated during difficult intra operative assembly of COC bearings (Langdown et al., 2007).

In general, one can discriminate between particulate and soluble wear debris. Evidently, particulate wear debris can be produced by any of the above described wear mechanisms while soluble wear can occur only by the corrosive wear mechanism and basically consist of soluble ionic forms of metals, either from the implant surface itself or from the surface of released wear particles. Particulate corrosion debris is also generated by an electrochemical process in which metal ions released from an implant surface subsequently form metal salt precipitates. Such corrosion products may be generated from any metal surface but most commonly originate from MOM modular interfaces (Urban et al., 2004). Importantly, the generation of wear debris in a prosthetic hip from different mechanisms (described above) can occur either simultaneously or at different times over the lifetime of the prosthesis.

6. Wear rates and the choice of modern bearings for young patients

In vivo measurements from tissue retrieval studies often report on the amount of the prostheses debris produced (either particle mass or particle number) per gram of dried

tissue. Such investigations have shown that the number of wear particles surrounding THRs can range from $8.5x10^8$ to $5.7x10^{11}$ per gram of dry tissue (Hirakawa et al., 1996). However, given that the concentration of wear debris decreases with increasing distance from the bearing surfaces and that a great amount of wear particles may not stay adjacent to the prostheses but rather be carried to very distant sites (see section 7), the adequacy of such measurements for the calculation of wear rates in vivo is questionable. Wear rates in vivo can be perhaps more adequately calculated using measurements of linear or volumetric wear from retrieved implants. Linear wear is reported in length units and values represent the depth of several ridges found on randomly chosen sample areas from the surface of retrieved components. Volumetric wear can be calculated from numerous linear wear measurements, using certain equations/formulas and assuming that the femoral ball (or acetabular lining) is originally a perfect sphere with a radius to best fit non-worn regions of each component (McKellop et al., 1996).

In vitro hip simulator studies report wear rates per million cycles (Mc), since 1 Mc is thought to correspond to an implant's moderate use for a year. In fact, such studies could be considered more accurate, since wear debris can in fact be collected. Wear can also be presented as weight loss and then converted to volumetric wear using the alloy's density. However, questions have arisen as to the correspondence between the wear particles generated in vitro and those observed clinically in vivo (Savio et al., 1994). Nevertheless, hip simulator studies have proven particularly useful in identifying the wear pattern/profile of total hip systems; thus such studies have shown that unlike MOP systems which show linear ratios of wear over time, modern MOM prostheses have an early high wear ratio phase (run-in) followed by a lower wear ratio phase (steady-state) (Anissian et al., 2001). The same biphasic profile is observed also with modern COC articulations (Hatton et al., 2002) and it is speculated that the initial wear phase is due to a polishing effect resulting from the motion of the head against the cup (Mode 1 wear) while the following phase is mostly due to third body wear. Hard-on-soft Charnley type couples like MOP have a single, constant rate of wear production since there is no 'polishing effect' i.e. it is the soft lining of the cup that always wears out.

PE wear rates from MOP articulations reported both in vivo and in vitro range in general from 30-100mm^3 per year. In the U.S., COP is the most common alternative bearing combination used in THR patients as it has been shown to reduce wear rates when compared with conventional MOP by 10% to 50% for periods exceeding 10 years (Jazrawi et al., 1998). However, other studies have not reported significant differences between MOP and COP wear rates (Schmalzried et al., 1998). Anissian et al calculated the run-in and steady-state wear rates of modern MOM articulations to be 2.22mm^3/Mc and 1.0mm^3/Mc, respectively. However, higher wear rates have been estimated from in vivo studies. McKellop et al concluded that the long term maximum wear rates of any design could be approximately 6μm per year - corresponding to a maximum mean volumetric wear of 6mm^3 metal particles per year (McKellop et al., 1996). One reason for the differences observed between in vivo and in vitro reported wear rates could be the nature of the lubricant used in simulators. The tribologic performance of a joint largely depends on the existence of a fluid (lubricant) film and the amount of coverage it confers to its surfaces and lubrication has a major influence on the amount of abrasive and especially adhesive wear (Walker, 1971). Another confounding variable appears to be the presence of surface coatings, which have been reported on both ceramic and metallic implants (Streicher et al., 1996, Lu & McKellop,

1997). It may be that the bearing surfaces in a hip simulator are actually articulating on such (smoother) coatings instead of the implant surfaces. Using low protein serum as a synovial fluid substitute, adding EDTA to reduce protein precipitates and running simulator tests at speeds that prevent heat generation are some of the modifications thought to result in decreased coating phenomena (Medley et al., 1996). Chan et al concluded that low surface roughness and small clearance between the head and cup are necessary for adequate fluid film lubrication and therefore for less wear production to occur; they suggested that if these parameters are optimal, all other engineering and manufacturing factors do not have a significant effect on the production of wear debris. Their simulator tests also showed that the volumetric wear of MOM articulation is 2000 times smaller than that of MOP articulation (Chan et al., 1999).

In more recent hip simulator studies a technique called microseparation is employed, where the ball and socket separate slightly during the swing phase of gait, to produce (higher) wear rates that are more relevant clinically (i.e. are similar to the ones reported in vivo). It has been proposed that microseparation could occur in any hip prosthesis and it may be involved in the initiation of 'stripe' wear, a small band of wear observed to occur around the rim of acetabular cups in retrieved COC hip prostheses (Mittelmeier & Heisel, 1992). Neck and socket impingement is another way of generating stripe wear (Nizard et al., 1992). Nevelos et al, by introducing microseparation of the COC prostheses, reproduced for the first time clinically relevant wear rates (typically 1-5mm^3 per annum), wear patterns and mechanisms (Nevelos et al., 1999). Other microseparation studies reported wear rates of 1-2mm^3/Mc (1.24mm^3/Mc for modern prostheses and 1.74m m^3/Mc for the first generation ones). The wear stripe often seen clinically on the femoral head was reproduced on both prosthesis types. The degree of rim contact depended on clearance and the authors postulated that clinically, microseparation may depend on factors like components' alignment, position, soft tissue tension and muscle forces. Interestingly, two size-ranges of particles were found under in vitro microseparation testing: small (nanometre scale) and large (micrometre scale) particles (Tipper et al., 2002). Nanometre sized ceramic wear particles were first described in periprosthetic tissues in a study that also revealed a bimodal size distribution of alumina ceramic particles in vivo (Hatton et al., 2002).

According to the above, it is evident that hard-on-soft Charnley type bearings demonstrate more wear for the same time period than hard-on-hard bearings (MOM and COC) as predicted, but are less susceptible to catastrophic failure. Modern hard-on-hard surfaces are mainly only sensitive to failure due to surgical technique (e.g. fixation, component positioning). Artificial hips that produce little wear are thought to be more durable and have a lesser risk for osteolysis, loosening and revision; hence, given a correct surgical implantation technique, modern hard-on-hard bearings are the preferred choice for younger, more active patients who have good quality bone tissue (Figure 1). Judging by wear debris production rate alone, ceramics provide the most desirable bearing surfaces (Savio et al., 1994) with alumina COC THRs having the lowest wear rates of any bearing surface combinations (Boutin et al., 1988). It has been calculated that the debris produced from an alumina-alumina THR where the femoral head is not too small, no stress risers occur from implantation, the acetabular cup is aligned properly, and an adequate clearance is maintained between the ceramic components may be as little as 1/4000 that of an equivalent MOP design (Sedel, 1992, Hamadouche & Sedel, 2000, Hamadouche et al., 2002).

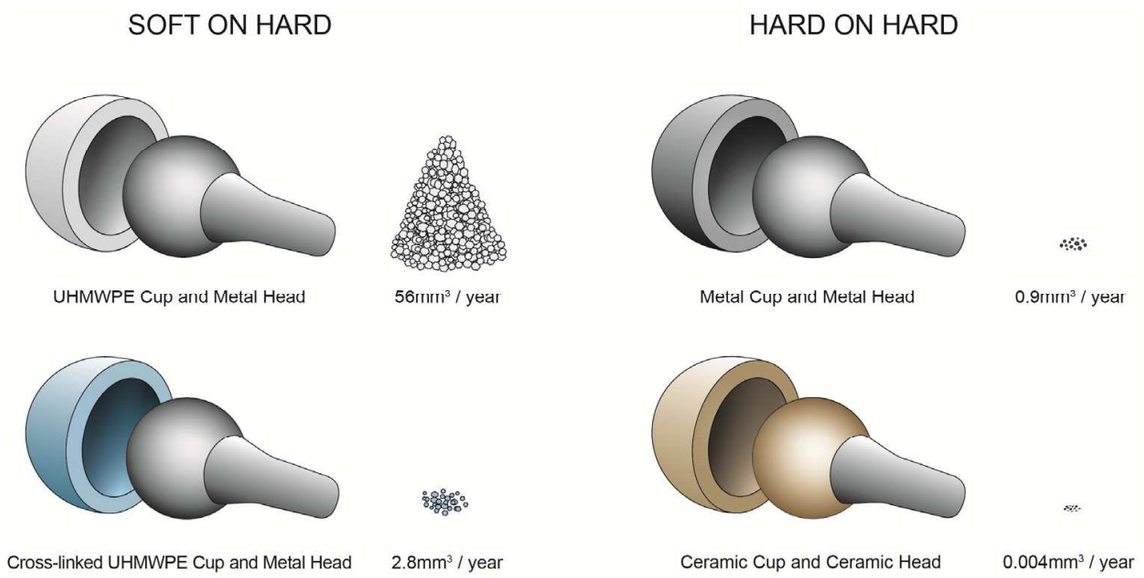

Fig. 1. Volumetric wear rates (estimates) of modern THR cup and head combinations. Data taken from Heisel et al., 2004.

Savio et al reviewed and compared descriptions of wear debris from many in vivo (revisions, autopsies) and in vitro (hip simulators) sources. The authors concluded that the type (composition) of THR materials plays a critical role in regards to the size, shape, volume and number of particles that are produced both in vivo and in vitro. More specifically, they hypothesised that the size of wear particles (minimum wear diameter) should be inversely proportional to a material's modulus of elasticity (i.e. its hardness) and they have consequently predicted that ceramic wear particles should be the smallest, polymeric ones the largest and metallic ones of an intermediate size (Savio et al., 1994). Simulator tests (Chan et al., 1999) support the above hypothesis and so do analyses of particles that are produced in vivo (Doorn et al., 1998). Nonetheless, hard-on-hard bearings, although producing far smaller volumes of wear than conventional Charnley type couples, may produce a similar active total surface area of debris. The very small (nanometre) size of metallic debris released by MOM bearings (Archibeck et al., 2000), combined with the fact that the bioavailability of metal is thought to be a function of the total surface area of the released debris rather than on its volume or weight (Shanbhag et al., 1997), casts doubt on the supposition that the net adverse biologic response will be reduced by modern MOM designs even though the volumetric wear is reduced. COC articulations are also reported to release nanometre sized particles (Hatton et al., 2002).

In addition to abrasive, adhesive and surface fatigue wear, metal alloys may suffer from corrosion. Corrosion can affect the whole surface of the implant or just a specific region (e.g. could be confined to an area of wear from mechanical stress). It is estimated that 30μg of metal ions (i.e. soluble wear) may be released from a prosthetic hip each day (Hennig et al., 1992, Merritt & Brown, 1996). Ions are shown to react with other molecules forming several types of particulate corrosion wear. Jacobs et al analysed particulate corrosion products from retrieved implants and surrounding tissues. Particles of metal oxides, metal chlorides, and chromium phosphate corrosion products were identified on implants of 10 designs

from 6 manufacturers. The most abundant solid corrosion product was an amorphous chromium orthophosphate hydrate-rich material (Jacobs et al., 1995).

7. Dissemination and biopersistance of wear debris from implanted artificial hips

As mentioned, wear debris can be both soluble (ions) and particulate. Ions may only be formed from metal components of artificial hips as they are the result of corrosion. Importantly, even in COC articulations, the stem is usually made of metal (Co-based or Ti-based alloy) and therefore, the existence of corrosion wear (both soluble and particulate) is applicable to all modern prostheses. Ions may stay bound to local tissue or bind to protein moieties that are transported via the bloodstream and lymphatics to remote organs. In an early post-mortem study, an increase in the concentrations of Co and Cr in remote tissues (liver and spleen) of a patient with bilateral Co-based alloy total hip components was reported; interestingly, Cr was found in a higher level than Co (Dobbs & Minski, 1980). Michel et al also reported on two post-mortem specimens with CoCr alloy components: in both cases high levels of Co and Cr were detected in adjacent tissues while a wide systemic effect was observed with increased concentrations of Co found in the heart, liver, spleen and lymphatic tissue and of Cr in the aorta, heart, liver, pancreas and spleen (Michel et al., 1991).

Elevated levels of Co and Cr ions in the serum, blood and/or urine of patients have been reported numerous times following both MOP and MOM THRs. In an early cohort study Black et al showed that Cr levels increased significantly (peaked) immediately after primary THRs; this peak was reduced six months post-operatively but it did not fall below control levels (Black et al., 1983). After a similar study, Sunderman et al suggested that a substantial increase of serum and urine Co levels seen in two patients was associated with loosening of their prosthesis (Sunderman et al., 1989). In a later retrospective study whole blood and serum were analysed from CoCr alloy MOP THR patients who had their artificial hips in place for up to 18 years. None of the devices were loose and no increase in the serum levels of Cr was documented, however, in 4 patients massive Co enrichments were seen as a consequence of implant corrosion while the levels of Co in the serum were significantly higher than controls up to more than 10 years postoperatively; moreover, significant Co and Cr enrichment was seen in several tissues and organs (Michel et al., 1991). Not surprisingly, joint failure can result in large increases in the amount of soluble metal ions detected in urine and/or blood (Jacobs et al., 1998a). According to Schaffer et al the levels of both Co and Cr in blood and urine increase continuously; at 2-3 years post-operatively more than a quarter of the patients retrospectively studied exceeded German occupational exposure limits (Schaffer et al., 1999). A more recent study showed a steady increase in both metal elements for up to 2-3 years postoperatively, depending on the type/brand of metal alloy, while subsequently metal levels declined although still remaining markedly above control levels (i.e. immediately after the operation). Thus, it has been proposed that the rises and declines of metal levels over time are the result of biomechanical influences on the implant's tribology (Lhotka et al., 2003). Simulation experiments support this view, since the pattern of metal levels observed in the blood and urine of MOM patients correlate with the (biphasic) wear pattern of the prosthesis per se (Anissian et al., 2001).

Importantly, Jacobs et al reported that younger patients had significantly higher levels of systemic metal release than older patients and postulated a more active lifestyle as the underlying factor (Jacobs et al., 1998a). A recent study by Dunstan et al in young (mean age 45 years) patients supports this view; moreover, it shows that MOM articulations released significantly higher levels of Co and Cr when compared to MOP ones while further elevation of metal levels was observed in patients with loose MOM THRs (Dunstan et al., 2005). Several in vivo and simulator studies have presented evidence that higher patient activity has as a result higher wear rates. Hence, it has been proposed that wear is a function of use, not time (Schmalzried et al., 2000). The case of a long distance runner with a MOM artificial hip supports this view: Metal (Co) levels in his blood were increased following completion of a marathon run and returned back to baseline levels 4 weeks later (Brodner et al., 2003). A contradictory study, after monitoring 7 recipients of well functioning MOM hips during a 2 week long physical activity challenge, suggested that serum metal levels are not affected by patient activity; therefore periodic measurements of serum ion levels could be used to monitor the tribologic (lubrication, friction, and wear) performance of MOM bearings without adjusting for patient activity (Heisel et al., 2005). However, the low number of participants, the use of only one external control and the fact that patients were not monitored past this period of physical exercise coupled with the existence of other contradictory reports (e.g. the case of the marathon runner) show that a correlation between MOM patient activity and systemic metal release can neither be proven nor excluded. When Jacobs et al explored the prospects for using blood, serum and/or urine metal levels to monitor the performance of MOM THRs, they concluded that it would be premature to recommend metal concentration analysis on a routine clinical basis since interpretation of values requires an extensive database with correlative clinical information (Jacobs et al., 2004). In summary, leaching of soluble wear (metal ions) following primary THR is not an occurrence of merely local significance, but one that affects the trace element status of the entire organism and over extended periods of time.

Particulate wear from artificial hip joints is also shown to be biopersistant and capable of systemic dissemination. Particulate corrosion debris (metal precipitates) from modular MOM junctions have been found locally and in sites remote from the hip (Urban et al., 1994). Cr phosphate particles have been found in the liver, spleen and para-aortic lymph nodes of patients with corroded but otherwise successful THRs (Jacobs et al., 1995). In a post-mortem study, Case et al reported an accumulation of wear particles in periprosthetic tissues and a systemic dissemination of huge numbers of sub-microscopic metal particles within the bone marrow, the local and distal lymph nodes, the liver and the spleen; in one case even in the frontal cortex of the brain. Interestingly, PE debris was not detected in these remote sites, despite its usual abundance in periprosthetic tissues, while the levels of metal were higher in the subjects that had a loose, worn implant (Case et al., 1994). A major parameter affecting the dissemination of particles in various tissues is their size; while bigger particles stay close to the periprosthetic tissues, smaller particles can travel further (Savio et al., 1994). Dissemination of THR metallic wear particles to the liver, spleen and abdominal lymph nodes was identified in other later studies (Shea et al., 1997, Urban et al., 2000). A recent post-mortem analysis showed that metallic particles were present in the liver and spleen of 73% of patients with a prior failure and revision of their THR. Particles generated by previous component failures were present in the liver or spleen a

decade or more later and suggesting that particle deposition in the organs is cumulative (Urban et al., 2004).

The dissemination properties and systemic effects of ceramic wear debris remain unknown. Because ceramics are insoluble in biological media (i.e. there is no production of ions/corrosion products at physiological pH), biocompatibility concerns do not relate to soluble wear debris. Although there are no reports of systemic dissemination of ceramic particles, ceramic particles have been observed in periprosthetic tissues (Savio et al., 1994). Similarities of their pale colour to the normal colour of tissues may mean that dissemination of particles to distant sites is harder to identify in the case of ceramics. The low wear rates and the very recent clinical use of COC articulations might also explain the absence of such reports. Based on reports on their observed size and shape however, there is no reason to believe that ceramic particles could not systemically disseminate and accumulate with time in various parts of our bodies, just as metal particles do.

8. Proposed links between total hip replacements and cancer

Given that wear debris from THR implants can disseminate (locally and systemically) and are biopersistant (mainly particulates), their carcinogenic potential is a real concern; especially as their use in younger patients, who may have a post-operative life expectancy of more than 30 years, is constantly increasing. Hard-on-hard bearings (i.e. MOM and COC) are usually the preferable option for such patients because they have been shown to generate less wear debris compared to conventional Charnley-type prostheses and are therefore thought to have less of a risk for early implant failure. But even for successful, durable THRs with minimal wear rates, the production and accumulation of wear debris over time cannot be avoided; and notably the use of a THR implant will inevitably be more rigorous and last longer in younger patients. The International Agency for Research on Cancer (IARC), a body within the World Health Organization (WHO) responsible for evaluating carcinogenic risks to humans, in a recent evaluation of surgical implants and other foreign bodies implanted (WHO, 1999) categorized all foreign bodies of Co-based, Cr-based and Ti-based alloys in Group 3, i.e. 'not classifiable as to their carcinogenicity to humans'. Ceramic implants were also under the same group.

8.1 Case reports, human cohort and epidemiology studies

There are relatively few reports of malignant tumours associated with total joint replacement (TJR) in humans, but the number of cases is increasing. Early published reports included cases of malignant soft tissue tumours such as chondrosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, osteosarcoma and haemangio-endothelioma associated with joint replacement surgery (Swann, 1984, Jacobs et al., 1992). These have led to calls for the establishment of a central registry for implant related tumours (Apley, 1989). In 1992, the editor of a well established orthopaedic journal wrote 'the 24 tumours thus far made public show no pattern in their histological type or in the timing of their appearance'. Nonetheless, he mentioned the importance of concerted efforts under way to accumulate cases of malignant neoplasms associated with TJRs, so as to better define the risks prospectively (Goodfellow, 1992).

During the past 30 years there have been sporadic case reports documenting the development of malignant neoplasms adjacent/proximate to artificial hips. Jacobs et al listed 18 reported cases in which malignancy was associated with MOM THRs. In most cases, malignant fibrous histiocytomas were reported at or near the femoral bone. The rest of the cases included osteosarcomas, fibrosarcomas or epitheloid sarcomas (Jacobs et al., 1992). Five years later, Cole et al listed 23 hip implant related tumours; malignant fibrous histiocytoma in ten patients and osteosarcomas in four while malignant epithelioid hemangio-endothelioma, chondrosarcoma, fibrosarcoma, synovial sarcoma, spindle-cell sarcoma, epithelioid sarcoma and an adenocarcinoma had each been reported once. Interestingly, only in two of these cases the acetabulum was the primary tumour site (Cole et al., 1997). A relatively large number of case reports have described neoplasms originating from bone or soft connective tissue in the region of metal implants. However, a recent analytical study did not report an increased risk of soft-tissue sarcoma after metal implants (Adams et al., 2003). Notably, the study compared the incidence of soft-tissue sarcoma after metal implantation to the general population's incidence of soft-tissue sarcomas, regardless of their presentation site. The results could possibly be much different if the comparison was made to the general population's incidence of soft-tissue sarcomas solely at the hip region. There are few well documented cases of malignant lymphoma following THR surgery. Radhi et al reported the only case of soft tissue lymphoma in the quadriceps muscle overlying an implanted hip 4 years postoperatively (Radhi et al., 1998). Ito and Shimizu reported a case of non-Hodgkin's lymphoma expanding from the ischium to involve the acetabular floor of an implanted THR (Ito & Shimizu, 1999). Ganapathi et al reported a B-cell lymphoma at the site of a chronic discharging sinus overlying a femoral periprosthetic fracture; the sinus formed at the time of the primary THR and continued to discharge for 12 years, until the patient died (Ganapathi et al., 2001). Other cases reported have developed after chronic osteomyelitis (Dodion et al., 1982). Lymphomas and other cancers developing at a site of a metallic implant may theoretically result from the carcinogenicity of the metallic alloy, in particular from prostheses made of CoCr. However, there is growing evidence that some soft tissue malignant lymphomas occur after long standing antigenic stimulation in patients with a defective immune system (Radhi et al., 1998). Startlingly, regarding ceramics and carcinogenesis, there has been only one case report on an aggressive soft tissue sarcoma 15 months after implantation of a ceramic Ti-stem COP THR (Schuh et al., 2004). However, this could be due to the fact that COC articulations have only recently been re-introduced for clinical use, therefore there is a limited experience with ceramics in comparison to metals.

It has been suggested that given the small number of reported cases of tumours around THR implants over the vast number of THRs performed, an association between joint replacement and local malignancy may be coincidental (Goodfellow, 1992). However, if one considers that wear debris from hip prostheses do not stay bound to periprosthetic tissues but disseminate throughout the body and accumulate in tissues/organs far from the hip, it is evident that looking for tumours only adjacent to the prostheses to draw conclusions as to the carcinogenicity of THR implants is not enough. To establish whether a link exists between such implants and malignancy, one must look at large scale epidemiology studies. In 1988, Gillespie et al studied more than 1000 patients and acknowledged the incidence of cancer 10 years after total hip replacement. There was a 3-fold increase in the prevalence of leukaemia and lymphomata in patients with Co-alloy THRs along with a puzzling decrease

in the incidences of breast and colon cancer. The authors hypothesised that chronic stimulation of the immune system from soluble and particulate wear of metal-on-metal THRs could encourage the emergence of lymphoreticular malignancies but increased immune surveillance could also inhibit the development of certain epithelial cancers (Gillespie et al., 1988). In a follow-up study, Visuri et al reported similar findings (Visuri & Koskenvuo, 1991). A later cohort study (Mathiesen et al., 1995) failed to confirm an increased prevalence of haematological malignancies following THR however, the number of patients followed was small and the post-operative follow up period of the patients was rather short. Nyren et al included a greater number of patients but still failed to link haematological malignancies with MOM implants. Instead, the authors reported a small but significant increase in kidney and prostate cancers in patients with THR (Nyren et al., 1995). A more recent study with over 400 patients, compared the incidence of cancer (9.5 years post-operatively) in patients with MOM or MOP articulations with that of the general population. Supporting Gillespie's puzzling findings, the authors reported that the total cancer incidence in both groups of patients was less than expected in the general population. Nonetheless, a significant increase in the incidence of leukaemia and lymphomas was shown for patients with MOM prosthesis only (Visuri et al., 1996).

In 1996, Gillespie et al presented an overview of the 4 relevant epidemiological studies published before mid 1995 with conflicting results. The results of the two earlier studies (Gillespie et al., 1988, Visuri & Koskenvuo, 1991) suggested a sustained increase in the risk of lymphoma and leukaemia after THR while the results of the two more recent studies (Mathiesen et al., 1995, Nyren et al., 1995) did not confirm this; although in one of them an increased risk was observed in the first year after implantation. The authors mention that 'the heterogeneity may be statistical in origin, but could also have a biologic explanation in the greater proportion of metal on metal prostheses used before 1973 (Gillespie et al., 1996). Gillespie et al had also performed 2 matched cohort studies and a case control study. In conclusion, neither the results of the matched studies of patients (operated on after 1973) nor the results of the latter 2 published epidemiological studies indicated a significantly increased risk of lymphoma or leukaemia following THR. Nonetheless, Gillespie et al tactfully advised that 'if metal on metal articulations were to be reintroduced, careful surveillance would be essential'. As joint replacement surgery is becoming one of the most common surgical procedures, the widespread epidemiological debate on the frequency of haematological malignancies in these patients remains to date.

The IARC has recently reviewed the epidemiological data for the risk of malignancy after THR (McGregor et al., 2000). It was noted that epidemiology studies compared patients with orthopaedic implants with the general population, thus failing to take into consideration several possible confounding factors/variables (e.g. immunosuppressive therapy, prevalence of rheumatoid arthritis). Moreover, the follow up period of most studies was considered to be too short after exposure to investigate the development of cancer, as carcinogens usually have a long latency period (i.e. the time from exposure to a carcinogen until the clinical presentation of a tumour/malignancy). Asbestos particles for example are known to produce cancer between 22 and 37 years after exposure (Barrett, 1994). It was also noted that the mutagenicity and carcinogenicity of biomaterials are influenced by their exact composition, their surface properties, the composition and rate of release of leachable materials, the physical environment and degradation (which may lead to formation of

compounds with different mutagenic properties). Therefore, since most epidemiology studies of orthopaedic implants have not taken into account the type of metal alloy used in each case, most of this information was considered inadequate. Unfortunately, no epidemiological data relevant to the carcinogenicity of ceramic implants is available to date. Therefore, orthopaedic implants according to IARC remain non-classifiable (WHO, 1999).

In molecular epidemiology, the occurrence of DNA damage has been explored for its links to the development of cancer. The frequency of cells with structural chromosomal aberrations in peripheral blood lymphocytes is the first genotoxicity biomarker that has shown a clear association with cancer risk. In two separate large (>1500 subjects) cohort studies, the level of chromosomal aberrations in peripheral blood lymphocytes was measured in healthy individuals at the start of the study, and the development of cancer was monitored over several decades. High levels of chromosomal aberrations were clearly associated with increased total cancer incidence in one cohort and increased total cancer mortality in the other cohort, suggesting that DNA lesions responsible for chromosomal aberrations are clearly associated with cancer risk (Hagmar et al., 2004). An important preliminary cohort study by Case et al used blood and bone marrow samples from 71 patients at revision arthroplasty and 30 controls (prior to primary arthroplasty) to test for chromosomal aberrations. Cells adjacent to the prosthesis had a higher chromosomal aberration rate compared to that seen in iliac crest bone marrow cells from the same patients at revision surgery. Both samples taken at revision surgery had higher chromosomal aberration rates than those seen preoperatively in femoral bone marrow cells in controls. The authors also noted the occurrence of clonal expansion of lymphocytes in 2 out of 21 patients studied at revision arthroplasty, which was performed more than 10 years after primary THR (Case et al., 1996). In a follow-up study, Doherty et al used peripheral blood lymphocytes from 31 MOM THR patients presenting at revision and over 30 controls (prior to having a THR) for cytogenetic analysis. They showed that at revision arthroplasty there was a 3-fold increase in aneuploidy and a 2-fold increase in random chromosomal translocations which could not be explained by confounding variables (smoking, gender, age and diagnostic radiographs). Most interestingly, metal alloy specific differences were seen: In the lymphocytes of Ti-alloy prostheses recipients there was a 5-fold increase in aneuploidy but no increase in chromosomal translocations; by contrast, in the lympocytes of CoCr-alloy recipients there was a 2.5 fold increase in aneuploidy and a 3.5 increase in chromosomal translocations. In lymphocytes from patients with stainless steel prostheses there was no increase in either aneuploidy or chromosomal translocations. Therefore, the authors suggested that although chromosomal translocations and aneuploidy can be seen in normal (non-THR) patients and are known to accumulate with time, genetic changes in THR patients may depend on the type of prosthesis (Doherty et al., 2001). Finally, in a more recent prospective study, Ladon et al investigated changes in metal levels and chromosome aberrations in patients within 2 years of receiving MOM THRs. A statistically significant increase of both chromosome translocations and aneuploidy was seen in peripheral blood lymphocytes at 6, 12 and 24 months post-operatively. The changes were generally progressive with time but the change in aneuploidy was much greater than in chromosome translocations. Although there was a significant increase of both Co and Cr ion concentrations, no significant correlations were found between chromosome translocation indices and Co or Cr concentration in whole blood while the clinical consequences of these observed changes remain unknown (Ladon et al., 2004).

8.2 Animal studies

In vivo investigations into the carcinogenicity of orthopaedic implant related materials were undertaken as early as the 1950s, prompted by the clinical observation that workers in nickel and chromate refining/smelting plants had increased risks of nasal and lung tumours. Oppenheimer et al were the first to clearly establish the potential carcinogenicity of implants: they placed various metal foils subcutaneously in rats and observed malignant tumours develop (Oppenheimer et al., 1956). One year later, Heath et al observed rhabdomyosarcomas following intramuscular injection of Co powder in more than half of the rats studied (Heath, 1957). Heath et al also demonstrated the development of sarcomata in rats bearing CoCrMo wear particles from total joint prostheses (Heath et al., 1971). However, tumourigenesis due to CoCrMo could not be confirmed in later studies by Meachim (Meachim et al., 1982).

Swanson et al were the first to test wear debris collected directly from orthopaedic implants. They used simulators to produce Vitallium (CoCrMo) powder, resuspended it in horse serum and injected it into rats; local sarcomas developed in 15 of 41 animals within 4-18 months (Swanson et al., 1973). In 1977, Gaechter et al used intramuscular implantation of solid alloy implants but, after evaluating seven alloys (260 animals in total) for 2 years, failed to demonstrate a carcinogenic hazard. Notably, they recorded 19 malignant sarcomas, all remote from the implantation site (Gaechter et al., 1977). In a follow up study, Memoli et al implanted rats with a variety of alloys in solid rod, powdered and sintered aggregate form and observed the animals (until they died or) for 30 months. A slight increase in sarcomata was noted in rats bearing metal alloy implants with high contents of Co, Cr or Ni and the development of lymphomas with osseous involvement was also more common in these animals. Interestingly, tumours were more commonly seen in rats that received (metal) powders compared to those that received rods or sintered implants (Memoli et al., 1986). Howie et al published a contradictory study on the effects of intra-articular CoCr-alloy wear particles in rats, where they noted no tumours after observing the animals for more than 1 year (Howie & Vernon-Roberts, 1988). Although carcinogenicity of various (mostly metal) implant materials has been documented in several animal studies, a more recent study investigating the carcinogenic effects of intra-articular powder administration of CoCrMo and TiAlV alloys in rats disputed these early findings, suggesting that such particles if carcinogenic are only weakly so (Lewis et al., 1995). The authors used particulate wear debris created in a simulator and observed the animals for 2 years (or until there was evidence of tumours). The negative carcinogenesis results of this study should be interpreted with caution, since the number of animals used per experimental group was low (8-12 rats), and the observation period was rather short. Bouchard et al assessed the carcinogenicity of CoCrMo versus TiAlV implants in a long-term study in rats. Importantly, the existence of implant associated tumours correlated with loose implants; none with well fixed in situ implants. Histologically the tumours were categorized as dermatofibrosarcoma, fibrosarcoma, malignant histiocytoma, lymphoma and osteosarcoma, seen both adjacent to the implantation site and in remote sites - most prevalent in the pituitary and mammary glands. The authors suggested a foreign-body (immunological) reaction as the primary mechanism of carcinogenesis, as a significantly increased accumulation of chronic inflammatory tissues was seen around loose rather than fixed implants (Bouchard et al., 1996). Animal studies using alumina ceramics as implant materials are virtually absent from

the literature, however, in one study in rats subcutaneous implantation of discs of aluminium oxide ceramic produced local sarcomas (Kirkpatrick et al., 2000).

There are many limitations as to what extent the carcinogenicity of human THR implants can be evaluated in animal studies. First of all, there are differences in the composition of the materials tested, although this is not surprising given the developments in the production of implants over the years. There are also some differences in the methods of preparation of materials for administration but mainly there is great variation in the proposed routes of administration and the site(s) of implantation. A priori, the intra-articular route of administration seems to be the most appropriate for arthroplasty carcinogenesis models and as early as 1988 intraarticular injections had been proposed as the route of choice for such studies (Howie & Vernon-Roberts, 1988). Furthermore, there is observed variation as to the physical form (foils, solids, particles) of the materials used and an increasing trend to use small particulates rather than solid implants; possibly since the important role of wear particles for implant failure in THR was recognized. Finally, the differences in the periods of time that the animals were observed following implantation and in the number of animals that were used in each case make critical evaluation of such studies difficult. The relevance of animal models for evaluation of THR cancer risk in humans is still questionable, especially as it is well documented that different animals and even strains/species of the same animal have different susceptibility to tumour formation (Gibb, 1992). Several calls and recommendations for the 'standardization' of animal carcinogenicity studies have been made (Courtland & William, 1996). Importantly, the IARC recently states 'despite the large number of animal studies, none have proven truly conclusive as to the carcinogenicity of implant materials, resulting only in indefinite statements at best regarding excessive tumour formation in animals exposed to wear debris from orthopaedic implants' (WHO, 1999).

8.3 In vitro studies

A cancerous substance is termed capable of inducing a cancerous phenotype; for in vivo evaluations this means the induction of solid tumours and/or haematological malignancies while in cell culture models scientists look for cancer biomarkers and/or neoplastic transformation. The latter is an attainment of certain heritable characteristics from a cell, such as loss of contact inhibition and continuous growth/division, which can lead to clonal expansion. Neoplastic transformation is often the result of one or more heritable genetic alterations and in fact all recognized carcinogens are also genotoxic. Thus, in vitro testing of potential carcinogens has initially largely relied on the use of several genotoxicity tests (e.g. the Ames test, which measures the ability of a chemical to induce mutations in bacteria). On the other hand, not all acquired genetic alterations lead to neoplastic transformation (i.e. cancerous phenotypes) hence not all mutagens/genotoxins are carcinogens. Concerns for the potential carcinogenicity of THR implants relate mostly to the systemic existence of both soluble and particulate wear debris for long periods of time following implantation. Even for successful THRs the generation of mode 1 wear from the intended ball-on-socket articulation (see section 5) is inevitable and so is its dissemination throughout the body. Currently, due to their low wear rates, the preferred articulating couples for implantation in young patients are MOM (mainly CoCr alloy) and COC (mainly alumina). Unlike ceramics, there is a long clinical experience with metals. However, the genotoxicity of orthopaedic metal alloys has been investigated in-vitro mainly by testing their soluble ions, since until

recently it has always being assumed that the effects of metal particles could be attributed solely to their ionic form(s). Lison et al have shown this to be a misjudgement when they showed that Co metal particles induced DNA damage via free radicals by a mechanism which was independent of the existence of soluble Co (II) ions; in fact they proved that Co atoms from the surface of the particle were able to reduce oxygen, thus forming reactive oxygen species (ROS) (Lison et al., 2001). Notably, there are only a few in-vitro studies relevant to the potential carcinogenicity of orthopaedic metals which employed metal particulates rather than their ions.

Particulate corrosion debris from metal bearings includes insoluble metal salts. Patierno et al actually indicated that the water-insoluble (particulate) Cr VI salts are more potent carcinogens than the water soluble ones, since only the particulate Cr (VI) compounds induced neoplastic transformation of mouse embryo cells (Patierno et al., 1988). In later studies, Wise et al used chromosome damage as a measurable genotoxic endpoint to study the genotoxicity of both particulate and soluble Cr (VI) in primary human bronchial fibroblasts at concentrations of low, medium and high toxicity. The scientists used lead chromate ($PbCrO_4$) and sodium chromate (Na_2CrO_4) as prototypical particulate and soluble Cr VI salts, respectively, to show that the amount of chromosomal damage increased with increasing concentrations after 24h to both compounds (and so did the cytotoxicity levels) (Wise et al., 2002). Other studies have showed that metallic Co particles were able to induce DNA breaks and micronuclei in human peripheral lymphocytes in a dose dependent manner (Anard et al., 1997, Van Goethem et al., 1997). De Boeck et al showed that despite a relatively large interexperimental and interdonor variability, the DNA-damaging potential of the Co-tungsten carbide mixture was higher than that of Co metal and Co chloride which had comparable responses (De Boeck et al., 2003). Metallic Co and its compounds without tungsten carbide are classified by the IARC as being 'possibly carcinogenic to humans' (WHO, 1991) while Co metal containing tungsten carbide was recently classified as 'probably carcinogenic to humans' (WHO, 2006).

Perhaps the most relevant study to the potential carcinogenicity of CoCr-alloy wear debris was performed by Davies et al; using primary human fibroblasts as a cell culture model the authors reported on metal-specific differences in the level/types of DNA damage induced by synovial fluid retrieved at revision surgery from 24 patients. Synovial fluid taken during revision surgery from all 6 samples from CoCr MOM prostheses and 4 of 6 samples from CoCr MOP prostheses, but none of 6 samples from stainless steel MOP prostheses caused significant DNA damage. Particulate-free samples of phosphate buffered saline where CoCr alloy was left to corrode also caused DNA damage and the authors suggested that this depended mainly on a synergistic effect between the Co and Cr ions produced by corrosion (Davies et al., 2005). Notably, the retrieved synovial fluid is thought to contain both soluble and particulate CoCr-alloy wear debris. Studies from our group have shown that CoCr alloy particles cause genotoxic damage in primary human fibroblasts while factors such as particle size and cell age may influence the genotoxic outcomes (Papageorgiou et al., 2007a, Papageorgiou et al., 2007b). There is a lack of in vitro carcinogenicity and/or genotoxicity studies for particulate alumina. Alumina's biocompatibility has been evaluated by Takami et al using the Ames test in bacteria; no mutagenic activity was observed in 5 tester strains of Salmonella typhimurium. In addition, no cytotoxicity was observed in mouse fibroblast cells following incubation with Al_2O_3 disks in cultures for up to 48 hours (Takami et al., 1997).

However, a more relevant study by Dopp et al reported that alumina ceramic fibres were genotoxic to human amniotic fluid cells causing both numerical and structural chromosomal aberrations (Dopp et al., 1997). More recently, our group has shown that alumina particles can be genotoxic to human cells in vitro (Tsaousi et al., 2010).

The cellular mechanisms of carcinogenesis have been the subject of a vast amount of in vitro studies in the field of cancer research. Such studies have elucidated the cause-effect links for most of the recognized human carcinogens. Interestingly, out of all listed carcinogens to date (according to the IARC), asbestos is the only substance of a 'particulate' nature. Studies investigating the effects of particulate matter in relation to lung cancer have shown that the carcinogenicity of particles and/or fibres follows different rules to chemical carcinogenesis. Particles and fibres form a rather specific group among all toxicants, and their physicochemical behaviour in genotoxicity tests is usually very different from that of soluble chemicals, especially the nature of their interaction with DNA. During/after exposure, chemicals may interact directly with DNA and/or indirectly (e.g. following metabolic activation and/or cell signalling events). On the other hand, particulate matter is thought to interact with DNA only following internalization (i.e. phagocytosis), while indirect action on DNA is possible without the need for metabolic activation (e.g. via formation of ROS related to surface properties and/or interaction with mitotic spindle apparatus). Another major difference is seen in the kinetics of exposure. Chemicals show a classical pharmacokinetic behaviour: distribution, biotransformation, elimination. Particulate kinetics on the other hand depends on deposition, clearance, durability, overload, etc. Furthermore, particulates are believed to have a 'carrier' function in vivo (Donaldson & Stone, 2003, Speit, 2002, Oberdorster, 2002).

Both CoCr alloy and ceramic THR systems are 'not yet classifiable as to their carcinogenicity to humans', although Cr (VI) is accepted around the world as a human lung carcinogen (WHO, 1990) and soluble Co (II) salts have recently been classified as possibly carcinogenic to humans (WHO, 2006). This may be in part due to the lack of enough convincing evidence that CoCr particulate wear debris can be genotoxic. However, for ceramic THR systems, the main reason is probably that they have only recently been introduced to the market. In vitro studies from our group have shown that both CoCr alloy and Al_2O_3 particles are genotoxic to human cells (Papageorgiou et al., 2007a, Tsaousi et al., 2010). Importantly, it has recently been shown that cobalt-chromium nanoparticles can damage human cells across an intact cellular barrier without having to cross the barrier, by intercellular signaling possibly through cell-cell junctions (Case et al, 2009).

9. Conclusion

THR is generally considered as a treatment option when pain is so severe that it impedes normal function despite the use of anti-inflammatory medication. As an elective procedure, it is a decision reached after careful consideration of its comparative benefits over its potential risks. When the editor of JBJS invited surgeons to submit reports of any tumour associated with replaced joints he wrote 'although the benefits of joint replacement might outweigh any risks a thousand-fold, that is no excuse for suppressing the facts'. As modern non-corroded MOM and COC THRs commonly used for young patients will still inevitably generate particulate wear over time, it is our belief that research should focus more on its long-term genotoxicity and therefore carcinogenic potential. The genotoxicity of different

materials should also be taken into account for the design and development of all prosthetic implants. Finally, THR surgeons should consider lifestyle factors further than the levels of physical activity such as the likelihood of having children.

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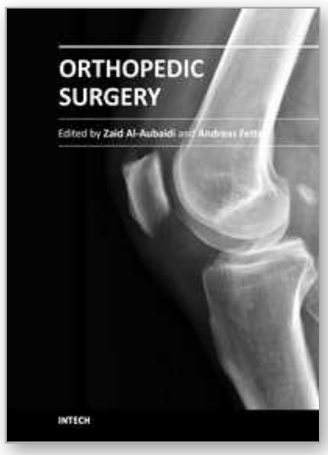

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Orthopaedic surgery is the widest and the strongest growing surgical specialty. It is clear, that the process of improving treatments and patients care, requires knowledge, and this requires access to studies, expert opinion and books. Unfortunately, the access to this knowledge is being materialized. As we believe that access to the medical knowledge should be reachable to everyone free of charge, this book was generated to cover the orthopaedic aspect. It will provide the reader with a mix of basic, but as well highly specialized knowledge. In the process of editing this book, my wife Jurgita has been, as usual, the most supportive person. I would like to thank her for being in my life. I would like to thank Mr. Greblo, the Publishing Process Manager, for all his help and last but not least thanks to our readers, as without them this book would have no meaning.

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