Chapter 1

Introduction

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Arthritic changes in hip and knee cause considerable disability and can lead to social isolation[1]. The development of an operative treatment that both relieves pain and restores motion has therefore been of paramount importance to many patients suffering from osteoarthritis, rheumatoid arthritis, and arthritis secondary to other causes. The improvements in physical functioning are sustained in the long-term[2]. The total hip replacement (THR) has therefore been referred to as "the operation of the century [3]."

History and development

After attempts at resurfacing the arthritic hip with fascia lata, skin and submucosa of pigs bladder, Smith Petersen covered the reshaped femoral head with vitallium. This is seen as the beginning of a new era of arthroplasty.

Wiles[4] was the first to develop a total hip replacement in 1938, but total hip replacement was revolutionized by the invention of the low friction arthroplasty by Charnley (Fig.1) in 1961[5]. He introduced the concept of low frictional torque forces, fixation of the components using acrylic cement, and the use of high-density polyethylene as a bearing surface. These new elements finally guaranteed longevity in THR, leading to reported survival rates of 77% and 81 % after follow-up of 25 years[6,7].

Fig.1 *John Charnley*

McKee (Fig.2) and Watson Farrar[8], realized that the Thompson and Austin-Moore metal femoral head replacements were only tackling half of the problem and introduced a ball and socket type of artificial joint with cobalt-chrome components in 1951. The first type was used as a cementless implant, but the implant was not stable and early loosening was the result. They followed Charnley and started using acrylic cement. The cup could now be sunk deep into the acetabulum, which facilitated the use of a larger, more anatomical head size. Although they realized the larger head could possibly cause more wear, they believed that only a small amount of movement occurred during weight bearing, with frictional forces at their greatest. Frictional forces were believed to be diminished by the distraction of gravity in the non-weight bearing phase. They also knew from experiments done at Stanmore, that cobalt-chrome alloy had a very low friction coefficient.

Fig.2 *McKee and a McKee-Farrar THR retrieval.*

Müller developed another well-known THR, made of a chrome-cobalt-molybdenium alloy (Protasul®) to increase the strength of the stem, because breakage of the Charnley stem was one of the failure modes. He used polyethylene for the cup, just like Charnley, but preferred a somewhat larger head (32-mm) to the 23-mm Charnley head, because of the reduction in dislocation risk. An even larger head simply was not feasible, because the polyethylene had to have a sufficient thickness to be able to withstand the expected wear (1 mm per 5 years) over time.

Weber was another pioneer in the development of THR. He worked with Charnley and Müller, from whom he picked up many ideas. When he became director of the orthopaedic department in Sankt Gallen, Switzerland, in 1967, he put his ideas to the test and developed a stem made out of Protasul®, featuring a rotating trunnion to reduce friction in the ball and socket joint, thereby hoping to reduce wear and

mechanical loosening of the acetabular component. Although he originally started with a large polyester head[9], from 1971 onwards a metal 32-mm rotating head was used, articulating with a high-density polyethylene cup[10]. This became known as the Weber rotation prosthesis, which has been used as the standard prosthesis in the Binnengasthuis and later the Academic Medical Center in Amsterdam since 1974. Apart from the mechanical benefits of the trunnion mentioned above, another benefit was the ease with which a femoral head replacement, used in fracture surgery, could be changed into a total hip replacement. The large fracture head was easily removed and replaced by a smaller 32-mm head after implantation of the acetabular component. The stem could be left in situ. To further reduce wear, a ceramic head was added to the Weber rotation hip system in 1973.

Weber was again at the forefront of orthopaedic innovation when he realized that the metal-metal articulation of McKee and Watson-Farrar produced little wear and introduced Metasul[11], starting a renewed interest in metal-metal articulations.

This introduction is not meant to be a complete summary of all the historic landmarks in the development of the total hip replacement, but these pioneers paved the way for a very successful procedure and inspired many others to perfect their invention.

Fig.3. *The Binnengasthuis in the city centre of Amsterdam as seen from the Grimburgwal*

Background concerning loosening of the implants

Loosening and implant-related factors: design and materials

By the end of the 1970's, clinical studies reported on cemented prostheses showing signs of loosening at follow-up[12-14]. Radiolucent changes around the components with or without subsidence of the implant were seen. This radiological phenomenon was related to osteolysis, which has now been more clearly defined as a process of: "progressive destruction of periprosthetic bony tissue characterized on serial radiographs by progressive radiolucent lines and/or cavitation at the implant-bone or cement-bone interface." Radiolucency around femoral components can be classified as linear (equally distributed around the prosthesis) or focal (islands of bone loss or cavitations) in close relation to the implant.

These changes were initially believed to be the result of infection, but cultures did not reveal any growth of bacteria[15]. In 1976, histological examination of tissue taken from these osteolytic areas showed the presence of cement-particles[16]. In 1977, Willert described the loosening of components as a result of a granulomatous tissue reaction induced by cement wear-particles[17]. This phenomenon was later called "cement disease"[18] an aseptic process, hence leading to "aseptic loosening". This led to the development and introduction of cementless THR-designs. Later, it turned out that not only cement particles, but polyethylene and metal particles also induced a foreign body-reaction, as became evident by osteolysis around uncemented designs. The term "cementless" disease was introduced.

Although improvements in surgical and cementing technique evolved, loosening remained a problem and various theories have been proposed since. Historically, the wear particle theory has been pre-dominant in efforts to comprehend this process of aseptic loosening[19] and has become an orthopaedic paradigm. As a result, research has been focused on the causes of wear, its mechanisms and the identification and development of wear-resistant materials.

The causes of wear are multifactorial and influenced by patient- and surgical factors as well as by the properties of materials used. Patient factors include the duration of use, age[20], general health and activity of the patient[21,22], whereas the influence of gender and weight are less evident. Surgical factors are increased cup inclination with apical loading and decreased cup anteversion with impingement of the stem neck[23,24]. Diminished wear rates can be realized by medializing the center of rotation[25], thereby increasing the stem offset and lever arm momentum. By mechanisms of wear (Table 1), the change in morphology of materials that cause wear-damage is described. The conditions, under which the prosthesis was functioning when the wear occurred, are referred to as wear modes (Table 2).

Mechanisms of wear	
Adhesion	This involves bonding of surfaces when they are pressed together under load. Sufficient relative motion results in material being pulled away from the surface, usually from the weaker material.
Abrasion	This refers to a mechanical process wherein asperities on the harder surface cut and plow through the softer surface, resulting in removal of material.
Fatigue	When local stresses exceed the fatigue strength of a material, that material then fails after a certain number of loading cycles, releasing material from the surface.

Table 1 *Mechanisms of wear*

Modes of wear	
Mode 1	Intended motion of two primary bearing surfaces against each other, e.g. motion of a femoral head against a PE liner.
Mode 2	Unintended motion of a primary bearing surface against a secondary surface, e.g. motion of a femoral head, which has penetrated through the PE liner against the metal shell.
Mode 3	Two primary bearing surfaces move against each other, with the interposition of wear particles creating accelerated wear (also known as "third-body" wear).
Mode 4	Two secondary bearing surfaces move against each other, e.g. the femoral neck impinging on the rim of the cup.

Table 2 *Modes of wear*

Research has focused on these issues, and tribology is the science that studies the properties of materials and interaction of surfaces in relative motion, including friction, lubrication, and wear. Over the years different materials, i.e. polyethylene, ceramics, and metal have been used for THR with the aim to decrease wear and loosening rates.

Fig 4. *Academic Medical Center, Amsterdam*

Polyethylene bearings

According to the Swedish Hip Arthroplasty Registry, the most frequently used THR is cemented with a polyethylene cup (PE), inspired by the success of the low-friction THR[26]. PE is a polymer and it is the most common particle type found in periprosthetic tissue. High-density PE (HDPE) was the first type used PE in THR and has a historical wear rate of 0.1 mm per year[27]. If wear simply were a linear process, it would take a century to erode through a standard size 10 mm thick cup. However, although linear wear may seem only a small problem, it has been estimated that billions of PE particles originate from the bearing surface per annum.

The resistance to wear of PE is influenced by many variables[28] e.g. type of resin, manufacturing method, methods of sterilization (e.g. gamma radiation in air produces oxidative degradation and aging of PE and this method was abandoned as of 1998), shelf-time (oxidation) and the degree by which polymere strains are bonded (cross-linked).

In our cohort, we have used an all polyethylene cup (RCH 1000; Chirulen®, Hoechst, Germany). Schüller and Marti[29] showed that after an average of 10 years, PE wear, using the metal rotating head of the Weber Rotation prosthesis averaged 0.96 mm with an average wear of 0.1 mm per year.

Ceramic bearings

Ceramics e.g. aluminumoxide (alumina), zirconiumoxide (zirconia) and silicon-nitride, are an attractive bearing material for use in THR because of its low coefficient of friction and high resistance to scratching. The disadvantage has been mainly increased brittleness and possible breakage.

Mittelmeier first used a double alumina bearing uncemented THR[30]. Problems with this concept were early loosening, possibly due to a difference in elasticity between the extreme hard ceramic and bone (which is more than hundredfold[31]), and component fractures. Later, comparison of cemented[32] and uncemented[33] alumina cups showed survival rates of 85% after 10 years and 64% after 1 year, respectively.

Although failure rates in these early series were relatively high, the ultra low wear properties of ceramic inspired surgeons to use ceramic heads in combination with polyethylene. Indeed, in our clinic, after 1978 ceramic/PE became our bearing of choice and wear in comparison to metal/PE was reduced to 0.26 mm at 10 years, with an average of 0.03 mm per annum[29]. Others found similar results as well[34].

Metal-on-metal bearings

This first generation metal-on-metal articulation, using cobalt-chromium[8] showed high loosening rates[35,36]. The metal-on-metal concept was therefore abandoned in the late 1970's and McKee himself stopped using his prosthesis in 1982. By then, the reasons of the high failure rates had become more apparent. They included technical production flaws, the use of an alloy with low carbon content, and the rim of the cup were in too close contact with the head leading to high frictional forces between the bearing surfaces and subsequently high torque forces between the components. These torque forces were higher than the bonding forces of cement[36].

However, in some designs where the point of contact in the bearing was between the apex of the head and the cup, the failure rates were lower[37,38]. Moreover, measurement of wear of McKee-Farrar prostheses retrieved after 20 years of use, showed a combined femoral and acetabular linear wear of 4 microns per year[39], which is about 25 times less than was radiologically measured in metal/PE bearings in Charnley prostheses[40].

These findings induced a renewed interest in metal-metal bearing. For instance, B.G. Weber from Switzerland introduced the second-generation metal-on-metal articulation in the 1980's, called Metasul ("Metalsulzer" from Sulzer Medica, renamed Centerpulse, now Zimmer, Warsaw, IN, USA). It is a wrought casted CoCrMo alloy, which is very strong, allowing thin cups to be used with large heads providing enhanced joint stability and range of motion[11]. Clinical success with Metasul® has been demonstrated in long term follow-up studies with a reported 0.2% incidence of mechanical loosening[41].

The small size of metal particles (less than 100 nanometer) is supposed to be advantageous, because they are below the critical size to induce macrophage reaction[42], which is considered a prerequisite for osteolysis. On the other hand, small particles can cross the blood-barrier leading to elevated serum and urine concentrations of both cobalt and chromium[43,44]. At present, it is still unclear what the long-term effects of those higher concentrations might be, and therefore some do not recommend the use of metal-on-metal bearings in fertile women.

Latest developments in tribological research

In the quest for better and more wear-resisting materials there are two main directions of research: (i) improvement of the wear properties of PE by "cross-linking" and (ii) investigation of alternative bearing materials such as ceramic-on-polyethylene, ceramic-on-ceramic and metal-on-metal articulation. These types of bearing cause less wear and produce smaller size (submicron) particles than PE, and might decrease the chance of a host reaction.

This process of "cross-linking" is an important development, which seems to reduce aging of PE. This process means that by ionizing radiation polymeric chains can "cross-link" and become more resistant to degradation by oxidation then conventional UHMWPE[45]. This highly "cross-linked" PE (HXLPE) has been on the market for clinical use from 1999 on. In vitro hip simulations[46-49], early and intermediate clinical studies,[50-53] and retrieval studies[45], have all demonstrated a reduction in wear of HXLPE as compared to conventional UHMWPE.

Already a second-generation HXLPE (X3-HXLPE) has emerged with seemingly even better survivorship in hip simulator studies[54].

Now that over the years, THR designs, cementing techniques and quality and strength of ceramics[55,56] have improved, alumina-on-alumina articulation has regained new interest and clinical results have improved[56,57]. It seems that alumina-on-alumina bearing has the lowest wear rate of all bearing combinations in clinical use[56,58,59]. In addition, in retrieval studies of failed alumina-on-alumina THR, the least amount of particles are found[60] and particles are not very biologically active[61,62]. One animal experiment showed less bone resorption and inflammatory response of alumina particles as compared to titanium and polyethylene particles[63]. The latest ceramics are "mixed" oxide ceramic (80% alumina and 20% zirconia)[64] and silicon nitride[65], and they have been found to have better mechanical properties than conventional alumina, after retrieval and after mechanical testing, respectively.

Experimental research is being done using diamond coated metallic surfaces: after 15,000,000 test cycles corresponding to 15 years of clinical use, no measurable wear was found[66,67].

Loosening and aseptic processes: current theories

Wear particle-induced osteolysis

Although materials have become more wear-resistant, particles are still generated. In vivo studies suggested that the presence of wear particles lead to a cascade of events resulting in bone resorption. On a cellular level, particles are phagocytosed by macrophages, which become activated[68] and release cytokines causing bone resorption, either directly or through osteoclast activation and osteoclastogenesis. In particular, polyethylene particles[69] and cement particles[19] were observed to possibly induce particle-induced bone resorption. However, some studies contradict these findings[70,71]. In vitro, particles have also been shown to inhibit osteoblast function leading to a decrease in bone formation[72].

On a biochemical level, soluble factors have been detected in the membrane surrounding loose prostheses that may cause bone resorption[73,74]. In retrieved interface tissue of aseptically loosened THR's from our cohort high cathepsin B activity was found[75]. These findings will increase interest in studying pharmacological agents that may modify such responses.

Next to these biological aspects of the process of loosening, mechanical aspects may be involved.

Insufficient initial fixation
Early loosening has been proposed as (mechanical) reason for late clinical loosening[76]. Fixation might have never occurred at the time of surgery, or might be lost shortly thereafter, due to improper implant sizing or flawed design, improper cementing technique, or inferior bone quality. Also, by preparation of the bone bed e.g. pressure-lavage or by thermal injury of cement, it is very likely that a superficial layer of bone dies[77]. Remodeling of this dead bone can subsequently lead to mechanical instability[78,79] and micromotion between bone and cement and/or implant is the result[19,80].

In animal models, such instability lead to the formation of a fibrous tissue interface between bone and a component[70,81]. Motion with compression of such an interface was observed to lead to bone resorption[70].

Stress shielding
Stress shielding may be another reason for loosening with both mechanical and biological aspects. Insertion of a component in bone can lead to bone loss according to Wolff's law which can be summarized as follows: bone will adapt to the load it is placed under. Thus, when loaded, bone will show remodeling over time to become stronger to resist the increased load. However, if the load decreases, the bone will become weaker during turnover as it is metabolically less costly to maintain and the stimulus to maintain bone mass through continued remodeling is absent. This phenomenon is known as stress shielding[82], because the load on the surrounding bone is partly taken over by the implant. Clearly, in stress shielding bone loss is not due to osteolysis. Stress shielding is associated with stiff(er) implants[83] and is seen when press-fit metal backed cups[84,85] and uncemented press-fitted stems[86,87] are used. In comparison, stress shielding is a not a phenomenon frequently seen with cemented polyethylene cups[88,89] or stems.

In our cohort, we consistently used a cemented PE cup for primary and, if necessary combined with a steel Eichler reinforcement ring in revisions. Both implant systems are thought to resemble the elasticity of bone (Young's modulus) to a more optimal degree. This was especially observed in cases when superolateral autologous grafts were used because coverage of the cup was less than 90 %.

Partial remodeling without resorption of the grafts in the weight-bearing zone was found by Marti et al.[90] which proves the absence of stress shielding of the grafts by the cemented PE implants.

High fluid pressure
Several reports suggest the physical influence of high fluid pressure on bone. Fluid pressures in pseudojoints after THR have reached 700 mmHg [91]. Ultrasound has shown that capsular distension caused by high intracapsular pressures is common in loose THR[92], and uncommon in cases without clinical signs of loosening. High pressures (500 mm Hg) have been measured in pelvic osteolytic lesions at revision surgery[24].

These findings were reason to further investigate the influence of fluid pressure by our experimental research group. Van der Vis applied an exogenous high fluid pressure in rabbits and established bone resorption[93,94]. An endogeneous applied pressure led to resorption as well[95-97]. These findings very strongly suggest that high fluid pressure may be one of the key factors in the loosening process.

Endotoxins
When standard cultures of specimens obtained from periprosthetic tissue around a loose component do not show growth of microorganism, most orthopaedic surgeons have the tendency to label that component as "aseptically loosened". However, sensitivity of standard cultures is reported to range between 65-94%[98], and polymerase chain reaction (PCR) has shown that DNA-remnants of bacteria are often found in these culture negative specimens[99]. These remnants are cellular membranes that contain antigens or endotoxins that can remain even after bacteria have been eradicated by the immune system or by antibiotics. In animal experiments, endotoxins have been found on used particles[100] and endotoxin-free particles produced less bone resorption[101]. From these data, it seems that particles are merely a vehicle, and that adherent endotoxins might be, at least partially, responsible for bone-resorption. The role of endotoxin contamination for prosthetic loosening is currently under investigation.

Theories of aseptic loosening: pros and contras

The findings of roentgen stereophotogrammetric analysis (RSA)[102] make it difficult to accept that wear particles *initiate* the process of component loosening. These studies have shown a higher probability of late clinical loosening when components migrate within 6 months after implantation[103,104]. This makes it more likely that loosening is initiated by mechanical causes, because generation of particles is a process that takes time and the amount of wear particles is unlikely to be high after such short period[19]. Migration of a prosthetic component can only be possible, when a fibrous tissue membrane surrounds the component. Consequently, there must be a correlation between late clinical loosening, migration of a prosthetic component and the presence of a fibrous membrane[76,105]. This fibrous membrane can act as an interstitial fluid compartment[96, 105] and at loading component micromotion can generate high fluid pressure (gradients). In an animal experiment, the fibrous tissue interface around a loose TKR exuded and imbibed fluid upon intermittent loading[106]. In the clinical setting, micromotion may very well lead to increased production of wear debris at the interface, but the influence of debris on loosening may therefore be secondary to the effects of micromotion and subsequent implant loosening.

Furthermore, pressure differences may induce a fluid flow towards the "effective joint space"[107]: the space around components, which is usually confined to the pseudocapsule. However, this effective joint space also includes the interface between prosthesis/cement, between prosthesis/bone, the membrane interpositioned, and small cement cracks in otherwise stable components[108], and bone cysts (such as in the retroacetabular bone adjacent to screw holes). This space is accessible to fluid with deleterious consequences due to influx of particles, cytokines and metalloproteinases as well as pressure effects[105,109]. Via this route even distant periprosthetic bone can be influenced by cellular, biochemical and physical factors[19, 107]. This can explain the distant local osteolysis in well-fixed stems[110], where pressure gradients may damage osteocytes[111] leading to bone resorption by osteoclast-mediated resorption[79].

In contrast to results of in vitro studies, most animal studies failed to establish particle-induced bone resorption and rather a decrease in bone formation was seen[70,71]. Other investigators did find particle-induced resorption[112] but could not reproduce their initial results[113]. In some studies, instability-induced resorption may have been misinterpreted as particle-induced resorption[114].

In clinical studies, some found a correlation between the amount of wear(-particles) and aseptic loosening of components[115,116]. The difficulty of interpreting these results is that the question: "did wear induce loosening or did loosening induce wear?" remains[76].

Based upon these findings the wear particle-induced loosening theory comes under siege. The loss of bone around an implant may be primarily the result of bone resorption due to mechanical factors whereas the (later) presence of particles could add to the loosening process by inhibiting formation of bone.

Loosening and infection

In the early days of prosthetics, infections frequently ended with a Girdlestone hip. Since then, there have been many improvements in prevention and treatment of prosthetic joint infection (PJI). Nowadays, most infections can be cured, enabling the patient to retain their hip implant. Still, PJI remains, after aseptic loosening, the second most common cause of implant failure[117] and is associated with high morbidity and high health care expenditures[118].

Prevention

Charnley's early experience with THR, at the end of the 1950's, yielded an infection rate of almost 9%[119]. His efforts to lower this unacceptable high rate resulted in a reduction to 1.3% over the next few years[119]. The decline of infection, in his view, was primarily related to the use of a laminar airflow system and a body-exhaust operative suit[119,120].

A prospective, randomized, multicentre study that was conducted by the end of the 1970's, showed that the use of ultra clean air in the operating theatre was associated with a clear reduction in infection[121]. Prophylactic antibiotics were not used in the initial studies of THR. After some early debate it became clear that prophylactic antibiotics were extremely effective in lowering the prevalence of infection[122-124]. In a study by Lidwell et al, it was shown that when laminar airflow was used in combination with prophylactic antibiotics the prevalence of infection could be reduced even further[125]. Cephalosporins remain the agents of first choice due to their broad-spectrum activity, low toxicity, and high tissue concentrations that are achieved. With this regimen a prevalence of deep infection after THR of 0.27% has been reported[126].

Besides the use of a laminar airflow system and prophylactic antibiotics[124,127], the more careful selection of patients, the elimination of remote infections[128], and the limitation of "traffic" in the operating room have contributed to lowering of the rate of deep infection. The current rate is 1 % after primary[129] and 3-5 % after revision surgery[127,130,131] in centres that perform arthroplasty surgery on a large scale. Indeed, by using those means in our entire cohort of primary THR reported on, the prevalence of deep infection was kept at a low 1 percent (D. Haverkamp, unpublished data).

Biofilm and antibiotics

Infection that is associated with prosthetic joints is typically associated with bacteria that grow in biofilms. Bacteria can attach to the surface of foreign body and produce a highly hydrated matrix of polysaccharide and protein. This substance together with the embedded bacteria is collectively known as a biofilm[132]. All bacteria are capable of producing such a biofilm and the less virulent microorganisms do this to a higher degree. Biofilm-associated bacteria are more protected against antibiotics and the host immune response than planktonic bacteria[133]. Biofilms may act as a nidus for recurrence of infection when antimicrobial therapy is discontinued.

Antimicrobial agents effective against biofilm-producing bacteria have improved outcome in treatment of PJI. For staphylococci, rifampin (also known as rifampicin) has been proven to be effective in vitro and in animal models[134,135], and in clinical studies[136,137]. Rifampin should not be used as a single agent because staphylococci rapidly develop antimicrobial resistance[138]. For gram-negative bacilli, chinolones (e.g. ciprofloxacin) are useful agents[136,137].

For several microorganisms that cause PJI (MRSA, funghi, enterococcus species, small-colony-variant *Staphylococcus aureus*, rifampin-resistant *Staphylococcus aureus, Pseudomonas*) there are no antimicrobial agents available that have good bioavailability, are effective against biofilm, and are well tolerated at the same time. In order to eradicate these pathogens, most likely the antimicrobial treatment should be administered in the absence of a foreign body e.g. prosthesis. For these reasons one can refer to these microorganisms in orthopaedics as "difficult-to-treat" microorganisms. They account for about 10% of all causative pathogens of PJI.

Clinical presentation and classification

A widely accepted classification for PJI is that of Coventry[139]. It uses the period of interval between the operation and the first manifestation of infection. PJI is classified as early (those that develop less than three months after surgery), delayed (3 months to 2 years after surgery), or late (more than 2 years after surgery). Early infections are typically manifested as an acute onset of fever, joint pain, effusion, erythema and warmth at the implant site, and are commonly caused by virulent microorganisms such as *Staphylococcus aureus*, ß-haemolytic streptococci or gram-negative bacilli. During the course of infection, cellulites or formation of a sinus with purulent discharge may occur.

In patients with delayed manifestation, the (low-grade) infection usually has been simmering for several months, giving rise to subtle signs and symptoms such as early implant loosening or persistent joint pain (also at rest). The involved pathogens, such as coagulase-negative staphylococci, *Propionibacterium acnes* and *Corynebacterium spp.*, are less virulent. Early and delayed infections are usually acquired during implantation of the prosthesis via the exogenous route. Early infections that are acquired via the hematogenous route are rare, and for example are caused by an acute urinary tract infection.

Late infections are predominantly acquired by hematogenous spread from a distant focus[128]. A late infection can first manifest itself acutely in the form of sepsis, leading to an acute onset in the affected joint, or else can start gradually and lead to a deep-seated abscess.

Diagnosis and definition of PJI

The diagnosis of PJI is straightforward whenever there are specific signs of infection i.e. a sinus tract or frank purulence around a component at the time of surgery. More often though, the presentation of PJI is variable, and resembles that of aseptic loosening. PJI is suspected when there is a history of persistent wound drainage after surgery[140], pain at rest, elevated laboratory signs of infection or radiological signs of early component loosening sometimes with periostal bone formation[141]. In diagnosis of PJI, current microbiology laboratory methods depend on isolation of a pathogen by standard cultures. The reference standard for diagnosis of prosthetic joint infection is growth of microorganisms in culture, as well as the presence of granulocytes in tissue on histopathologic examination. These standards are used

to define the validity of other tests. The use of swabs should be avoided because sensitivity is reportedly low (range 0 to 23%[98]). Culturing of tissue specimen has yielded the highest sensitivity (range 65 to 94%[98]). Nevertheless, sensitivity is not ideal. Hence, several investigators have come up with useful criteria for definite PJI, that include information on patient history, clinical signs and results of laboratory, microbiological, histopathological, radiological and nuclear examinations[142-144].

To further improve the diagnosis of PJI, culture-independent molecular methods have been developed. Broad-range polymerase chain reaction (PCR) is a molecular diagnostic method that allows for replication and amplification of genetic (DNA) material. This method was invented by Kary Mullis[145], for which he received the Nobel Price in chemistry in 1993. Since then, PCR has been applied to detect bacterial DNA in tissue and causative pathogens have successfully been identified in organ[146] and native joint infections[147], even when conventional cultures remained negative. Although PCR has been advocated as a useful diagnostic tool for detection of PJI by some[99] , this issue is still a matter of debate.

Surgical treatment of PJI

The goals of treatment of PJI are the eradication of infection and reconstitution of function of the affected limp. The mainstays of treatment are the operative debridement and antibiotic therapy regardless of how the infection is classified. Collaboration with an infectious disease specialist and/or a microbiologist with special interest in PJI's is often required to define the appropriate antimicrobial therapy. Surgical treatments include a two-stage exchange, a one-stage exchange, debridement with retention of the prosthesis, resection arthroplasty and amputation. Debridement includes removal of hematoma, fibrous membranes, sinus tracts, and infected and devitalized tissue.

The classic treatment for deep infection has been a two-stage exchange with removal of all foreign body material, collection of tissue specimen for microbiologic and histopathologic examination[148], a debridement, a 6-8 week lasting Girdlestone situation often with traction-suspension, and total duration of administration of antibiotics of three months[149]. The success rate with this regimen has been reported to range between 82 and 96%[149-157]. Patients with deep infection in our cohort were treated with this approach with satisfying results. In the rare situation when infection could not be controlled or in case of a lack of bone stock or gross muscle damage, a definitive Girdlestone procedure was performed with a relatively satisfying result[158].

Although the control of infection after two-stage exchange is generally good, the disadvantages of this approach are the longer immobility and hospitalization, and the higher morbidity and costs. Hence, a one-stage exchange would be preferable for patient and economic reasons.

Series of one stage revisions, with direct exchange of the implant and debridement, have reported a rate of cure between 76% and 100%[143,159-165]. Guidelines for selection of patients for a one-stage exchange have been proposed[160,166], that include (i) the presence of intact or mildly damaged soft tissues, and (ii) no involvement of difficult-to-treat pathogens. Such patient selection has lead to less recurrence of infection after 1-SE[143,160,165,167].

Successful results of debridement with retention of the implant also require careful patient selection[166]. Good results can be achieved when (i) the episode is classified as an early or late hematogenous infection with duration of symptoms of less than 3 weeks[137], and (ii) the implant is stable, and (iii) no difficult-to-treat pathogen is involved, and (iv) the soft tissue is intact or slightly damaged[143].

Ideally, management of PJI should be standardized. Unfortunately, at present this is not the case because of the different clinical presentations and the lack of data from randomized, controlled trials. Over the last 25 years a treatment algorithm for PJI has been elaborated in the Kantonsspital Liestal[166], Switzerland, which is a tertiary care center for orthopaedic infections, in collaboration with the unit for infectious diseases, University of Basel, Switzerland. In this concept, the decision to perform a debridement with retention, a one-stage exchange or a two-stage exchange with or without spacer is based on several factors. Strict adherence to this algorithm has shown an overall success rate of 86% in curing the infection[143].

In reports of different treatment regimens for PJI, the infectiological outcome has been the topic of main interest. Patient satisfaction after hip surgery however, is highly influenced by the functional result[168]. The functional outcome of the abovementioned algorithm was therefore the subject of a study conducted by the Kantonsspital Liestal, Switzerland in collaboration with the Academic Medical Center, University of Amsterdam. In a secondary study, we studied the effectiveness of broad-range PCR in diagnosis of PJI in current clinical practice.

Loosening and obesity

Obesity has a negative influence on health and mobility. It has been proven that osteoarthritis of the hip joint requiring THR is more frequent in obese patients169 and the outcome of this procedure in these patients remains an issue of debate. A negative influence of obesity on the result of THR was not shown in short term follow-up studies[170-172], whereas to our knowledge no long-term studies on this topic exist. Nevertheless, a recent large international survey performed in 12 European countries among orthopaedic surgeons, revealed that 90% believes that the long-term outcome of THR is impaired by overweight[173]. In addition, the fear of complications is increased among surgeons. Over the years, we have regularly performed follow-up of patients who had received a THR. In this way, the long-term outcome of THR and its complications in obese patients could be compared to normal weight patients.

Cementing techniques

Although the use of acrylic cement, popularized by Charnley in the late 1950's improved fixation of the prosthetic implants tremendously, mechanical loosening still was a problem, which became especially apparent when THR's were used in younger patients. Apart from identifying flaws in the prosthetic designs, cementing techniques were also evaluated and changes were made to improve the adherence to bone.

Early or first generation cementing techniques involved little or no preparation of the bone bed, antegrade filling of the medullary canal and no pressurizing apart from fingerpacking[3]. Charnley purely saw it as a filling[174], which functioned as part of the prosthesis, adapting it to the femur of the individual patient. This way, there was a large contact area, without the peak stresses of an uncemented

prosthesis like the Thompson or Austin-Moore. Bonding to the bone by the acrylic cement was not considered a prerequisite for longevity. After reports of component loosening rates of 20% and more after 10 years in the late seventies, some surgeons abandoned cemented techniques. Others adapted their technique to improve fixation, especially on the femoral side. Although the literature suggests there are 3 generations of cementing techniques, it is hard to identify a standard second generation cementing technique. Several innovations were introduced during the 1980's, but not all innovations were implemented by every surgeon and because different prosthetic implants were also used, comparison of outcome between patient groups because of these "improvements" need to be interpreted with caution. Even using an improved technique by the same surgeon, using the same implant is not without bias, because the surgeon will learn from experience.

However, the results of improved cementing techniques cannot be ignored. Mulroy and Harris[175] for instance, reported a 3% femoral loosening rate in 105 hips after a minimum of ten years. Their improved cementing technique entailed using a cement gun, an intramedullary polymethylmethacrylate plug and stems of improved design. Pressurization was not used.

Kaplan-Meyer analysis of 169,000 hips from the Swedish hip registry between 1992-2006 showed a survival of 86.6% (± 0.9 %) after 15 years, using high-pressure techniques for the femoral side in comparison to 85.1% (± 1.0%) in the hips without the use of this technique. This difference in outcome was statistically significant ($p<0.001$ Log rank).

Third generation techniques further include pulsatile lavage, reduction of cement porosity (vacuum mixing), and precoating of the stem[176]

Although many authors reported on modernizing cementing technique for the femoral component[175,177-181], papers on improved fixation of the acetabular component are scarce. Because of the persistent inferior results produced by cemented fixation of the acetabular component in comparison to the improved results of stems that were cemented according to improved techniques, several authors abandoned cemented fixation for the cups. The combination of a cementless cup and a cemented stem is known as a hybrid hip.

The difficulty in cemented fixation of the cup is the reproducible formation of good initial stability through an interlock between the cement and the bone, especially in the craniolateral part of the acetabulum. Radiographic studies have shown that the presence of a radiolucent line in zone 1 (deLee and Charnley[182]) increases the chances of failure of that cup 40 fold[183]. A good bony interlock provides stability necessary to withstand the elastic deformation forces of the acetabulum. This changes from a high oval shape to a spherical shape during weight bearing[184].

The bony interlock stiffens the periprosthetic bone, creating a stabile interface between cement and bone to withstand these plastic deformation forces. Apparently in a well-cemented polyethylene cup, some plastic deformation should be possible, because cementing metal backed cups into the acetabulum produced worse results. If the implant is too stiff (large difference in elasticity moduli), stress shielding is usually the result in the dome of the acetabulum. This bone loss can eventually lead to weakening of the bone that is supporting the implant and eventually to loosening.

Bleeding from the bone bed and insufficient removal of fibrous tissue and necrotic bone fragments from the interface are the main reasons for failure of establishing a good bony interlock. These are the main features that need to be addressed in any attempt at improving cementing technique. Using adrenaline soaked gauzes and creating a hypotensive state in the patient[185] can reduce bleeding. Pressurization of the cement is necessary to overcome the patient's blood pressure and reduce the amount of blood leaking into the interface. The shape of the acetabulum unfortunately does not allow for the kind of pressures that can be produced when the femur is distally plugged and proximally closed off by a pressurization device. The cementing technique of the acetabular component used in the Binnengasthuis and Academic Medical Center is described in chapter 5 and is combined in this chapter with the long-term results of cemented acetabular fixation.

These factors that compromise a good cement-bone interlock, are not an issue in cementless fixation of the cup. Good initial fixation in uncemented THR is usually reached by press fitting the cup, if necessary aided by screws or in case of screwcups like the Zweymüller® (Zimmer, Warsaw, Indiana, USA), by screwing the cup into the bone. Fixation is later enhanced by ongrowth of bone, which may be enhanced by coatings like trabecular metal or hydroxyapatite[186].

Design changes in cemented THR

Apart from changes in cementing techniques, implant designs were also changed to improve initial stability. Two types of stems evolved over the years, both successful, but very different in design. On the one hand, there are the stems that provide good initial stability within the cement mantle usually with a roughened finish and geometric shapes that control axial rotation (composite-beam or shape closed designs). On the other hand, there are smooth surfaced implants that allow for some controlled subsidence within the cement mantle (taper slip design).

The design of the cemented cup did not change much over the years, although a flange was added to some cups to improve pressurization of the cement. This was studied in cadavers and seemed to produce a more even distribution of the cement[187], but a later study showed no significant difference in the average penetration of cement into the bone[188].

Straying from cemented fixation

Due to disappointing results in the late 1970's and the association of periprosthetic osteolysis with the use of cement ("cement disease"[17]), cementless designs were developed, believing that by removal of the apparent cause of cement disease this would lead to a longer lasting fixation.

The hybrid hip[176] was developed because of disappointing results of the acetabular fixation with cement, whereas improved cementing techniques on the femoral side resulted in a better outcome. A cementless cup was therefore combined with a cemented stem.

Uncemented stem designs[189] can be divided into three categories: anatomic, tapered and cylindrical. Anatomically shaped stems showed a higher percentage of thigh pain[189,190], when compared to tapered or cylindrical designs. Cementless stems also led to proximal stress shielding. Proximal stress shielding and thigh pain were found to be related to a greater difference in elasticity modulus between the stem and the surrounding bone and to distal porous coating and increased diameter of the distal part of the stem[191,192]. Later designs therefore were made of titanium instead of cobalt-chrome, because of its lower elasticity modulus. They featured a porous coating on the proximal part of the implant only, and stiffening of the distal part, without increasing the diameter.

Uncemented cup designs are usually hemispheric in design or sometimes conical with a thread for screwing the cup into the acetabulum. The most used cups now are hemispheric press-fit cups. Screws, pegs or spikes can enhance its initial stability. Later stability is enhanced by ongrowth of bone onto the porous, hydroxyapatite or trabecular metal coating.

The first generation cups suffered from malfunctioning of the locking mechanism of the acetabular liner[193-196], accelerated polyethylene wear, and extensive periacetabular osteolysis[197]. Screwholes were found to potentially increase the affective joint space, which could lead to retroacetabular osteolysis ("backside wear"). Therefore, screwless press-fit cups are preferred.

The difficult hip

From 1974, we have used the Weber rotating total hip replacement as the standard implant in primary THR. The wrought casted CoNiCrMo (Protasul10®) curved stem was available in 4 different lengths. In 1980, a straight stem was added to the range of stems. Three different necklenghts were available. A 32-mm head was always used, either metal (Protasul 10®) or Al_2O_3 ceramic (Biolox®). Although larger heads were supposed to create more wear[198], it was felt that the larger head gave more range of motion, decreased the risk of impingement and also enhanced stability. The trunnion design, with its secondary articulation between the head and neck, allowed for some telescoping motion (Fig. 5). Perhaps this enhanced stability from the larger head and the trunnion is one of the reasons for a low dislocation rate. Indeed dislocation of a THR was a rare phenomenon in our entire patient cohort.

There was a choice of hemispherical and flat cups, the latter to facilitate implantation of a cup into a shallow acetabulum usually found in dysplasia. The all-polyethylene cup and the grit-blasted stem were cemented, using low-viscosity Sulfix® cement. This system was not only used in primary THR, but it was also used for more difficult cases, like hips with insufficient bone stock (dysplasia, revisions).

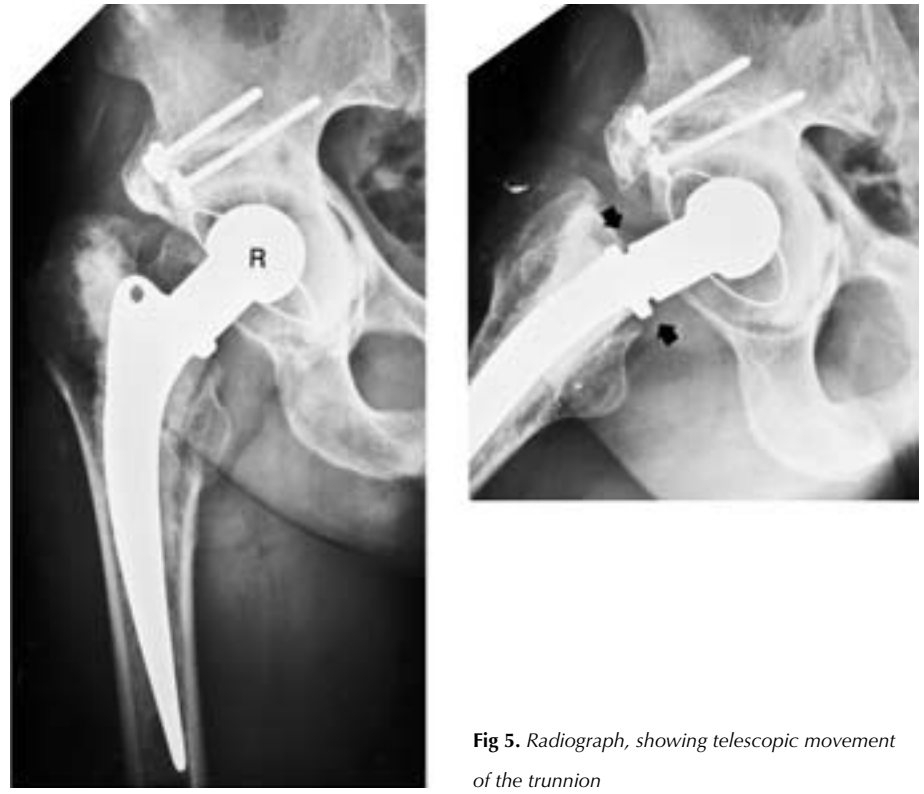

Fig 5. *Radiograph, showing telescopic movement of the trunnion*

An important factor in the survival of a total hip replacement is the surgical technique. This thesis presents several studies on the outcome of cemented THR in different situations, using the same implant (Weber rotation), and using the same surgical techniques and philosophy. The preservation of bone, the optimal usage of biological material (no waste), the creation of good coverage of the acetabular implant and the use of a standardized cementing technique are important items in this surgical philosophy. Other items like restoration of the centre of rotation and leaving the subchondral plate intact were also important items in the surgical technique.

Not only in acetabular dysplasia, but in all cases with an incomplete bony coverage of the acetabular implant, a roofplasty was added to the operative procedure. The addition of a superolateral bone graft decreased shear forces in a finite element study[199]. This decrease in shear forces would supposedly lead to a decrease in the risk of loosening. Bone grafts were usually taken from the excised femoral head, so no biological material was wasted[200].

We used small corticocancellous grafts instead of large bulky grafts, that were known to produce good short-term results, but failed in the long term. Another technique, using compacted morselized allograft was popularized by Slooff[201] from Nijmegen and Ling[202] from Exeter. Although this technique has been shown to have its merits[203-205], Marti and his staff did not adopt it due to satisfactory results with the triflange corticocancellous small bone grafts in acetabular reconstruction.

In revision surgery, bone stock can also be insufficient to support the implant. Therefore, everything was done during primary total hip surgery or even prior to that in femoral osteotomies, to ensure sufficient bone stock in case of future revisions[206].

In large segmental defects, an augmentation ring (Eichler ring) was used. This steel implant was not as stiff as other designs like the Müller, Ganz, and Burch-Schneider. Because of its lower elasticity modulus, there supposedly is less stress shielding, which allows for load transfer to the acetabular bone, and therefore presumably results in a better incorporation of superolateral bone grafts especially.

In osteoarthritis secondary to preexistent anatomic deformities of the femur, surgery can also be more difficult than in the average hip. These smaller, i.e. hypoplastic femora, usually have a narrow canal requiring a smaller than usual component. Our cohort contained 86 hypoplastic hips, often with muscle contractions and shortening of the leg. In all these cases, the combination of the smallest size off-the-shelf Weber rotation prosthesis, often combined with a superolateral roofplasty, proved to be a good solution. There never was the need for a custom-made stem.

New developments

Resurfacing and other bone preserving implants

The success of the THR and the growing confidence in its longevity led to the expansion of indications for hip replacement surgery. Especially young patients obviously demand more from their implants. As traditional stiff uncemented implants resulted in stress shielding of the proximal femur, also quite often with thigh pain, focus was directed towards designing implants that could be well fixed proximally. One of these implants was the Mayo hip® (Zimmer®, Warsaw, Indiana, USA). This short-stemmed implant, which gets its stability from a three-point

contact, might ultimately save femoral bone stock, especially in young patients for whom future revisions are to be expected.

Patient expectations have followed those of many surgeons, believing that full restoration of function should be possible, including sporting activity. To accommodate this, hip resurfacing was reintroduced. Earlier failures with resurfacing were ascribed to imperfect production of materials, leading to excessive wear and loosening. The idea behind resurfacing implants, like the Birmingham hip® (Smith&Nephew Inc, Memphis, Tennessee, USA) is that it restores normal anatomy and biomechanics of the hip joint and provides near normal proximal femoral anatomy and loading. Should future revision become necessary, most of the femoral bone stock is retained.

However, concerns have been raised about removing more bone on the acetabular side[207]. Other authors have not confirmed this, stating that with the possibility of choosing a femoral head size in small increments, the acetabular component need not to be larger than in a conventional uncemented THR[208,209].

Minimally invasive surgery

Since 2000, new processes in THR have been emphasized. Changes in pain management and anaesthesia were made to facilitate rapid recovery protocols. To further enhance a rapid recovery, minimal invasive surgery was endorsed, fuelled by the industry seeing opportunities to explore a new market. Minimal invasive surgery should not just leave a small scar to reduce self-consciousness of the patient, but should ideally produce less muscle damage and aid in a faster recovery. In a psychological study by Dorr in 2007[210], patients were very pleased with a small scar after 6 weeks, but at 6-12 months, the length of the scar was less important. Many minimal exposures have been advocated, like the two incision technique by Berger[211,212], the mini posterolateral incision[213], the direct anterior[214] and the modified anterolateral[215]. The best exposure is subject of debate, but in the end, the experience of the surgeon with a certain exposure and technique will dictate the outcome. One of the risks of minimal invasive surgery is the malpositioning of implants and risk of intra-operative complications, like fractures, because of the impeded view. Specially designed instruments and computer navigation can aid in decreasing these risks.

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Contents of this thesis

This thesis includes many studies focused on the longevity of the cemented Weber rotation total hip replacement, used in primary and revision cases. It also includes one animal experiment and one retrieval study, both dealing with aseptic loosening, and two studies on prosthetic joint infection (PJI).

In **Chapter 2**, we describe the long-term outcome of primary cemented THR after a minimum of 5 and a maximum of 20 years.

In **Chapter 3**, the treatment of osteoarthritis secondary to hip dysplasia is addressed. In most cases, the acetabulum was augmented by a superolateral bone graft. We present long-term outcome and describe the technique of bone grafting superolateral defects.

In **Chapter 4**, the attention is focused on dysplasia of the femur. In femoral dysplasia, the diameter of the femur is smaller and most often does not allow for a standard implant. We present a series in which we used the smallest size, standard stem of the Weber Rotation THR.

Chapter 5 focuses on the cementing technique of the acetabular component.

In **Chapter 6**, we present an experimental study in rabbits, in which the effect of mechanical compression of a fibrous membrane interface, on prosthetic loosening, is investigated. In addition, we administered high-density polyethylene particles to see whether their presence influenced the effect.

In **Chapter 7**, retrieved interface tissues from aseptically loosened THRs were studied for the presence of activated matrixmetalloproteinases (MMP-2 and MMP-9) and their relationship to macrophage activity and wear particles.

In **Chapter 8**, we show the results of a study performed to follow-up on an earlier study of cemented revision THR. We now present the results after a maximum follow-up of 24 years.

In **Chapter 9**, we analyzed the results after revision THR with an acetabular augmentation ring, which is used in cases with large segmental defects.

In **Chapter 10**, we deal with the supposition that overweight might challenge the outcome of a THR.

Infection is one of the most dreaded complications in total hip surgery. In **Chapter 11**, the functional, radiological and infectiological outcome after treatment of prosthetic joint infection according to a strict algorithm is evaluated.

In **Chapter 12**, the diagnostic value of the polymerase chain reaction (PCR) technique to detect orthopaedic infection is discussed.