Understanding the biological outcomes and responses to orthopaedic surgical implants.

Dr Catherine Bladen, University of Leeds, UK

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Acknowledgements:

Firstly, I would like to thank the Winston Churchill Memorial Trust for believing in my fellowship idea. Their support and encouragement has allowed me to undertake a truly life changing trip. Dr Marshall and I have made a significant and ongoing professional relationship that will facilitate cutting edge research in the field of orthopaedics.

Secondly, I would like to thank Dr Marshall and her surgical and research teams. Her work ethic and “can do” attitude has been truly inspirational.

Thirdly, I must say a big thank you to my parents, who looked after my children while I was away. Without them, this trip simply would not have been possible.
Overview:

The use of artificial materials in the treatment of arthritis over the past few decades has increased dramatically. It is important that we understand the biological responses to the materials used (metal, polymers, ceramic) and determine their effectiveness and suitability. It is important to understand the local and systemic effects of these implanted materials both at the time of implantation and indeed over the lifetime of the implant.

Total hip replacement (THR) is a surgical intervention eliminating pain and increasing mobility. Ultra High Molecular Weight Polyethylene (UHMWPE) prostheses are still the most frequently used worldwide. Most THR’s will fail (10-15 years) particularly in younger patients (<65 years) who often outlive the life of the implant. The major cause of failure is osteolysis and aseptic loosening due to the biological response to UHMWPE wear particles (i.e.) the activation of inflammatory cytokines including tumour necrosis factor-alpha. This fellowship brought together Dr Catherine Bladen (molecular biologist) at the University of Leeds and Dr Amanda Marshall (orthopaedic surgeon) at the University of Texas (San Antonio) who both have a primary research interests in the biological responses to wear particles from UHMWPE implants and in the development of novel bearing materials. Bringing together scientists from different disciplines has allowed for meaningful intellectual exchange and highlight possible future collaborations within this area of research.
Fellowship Itinerary:

Four incredible weeks were spent with Dr Marshall in the research laboratory and in surgery. Specifically the first week was spent with Dr Marshall in surgery observing hip and knee replacements. The second week was spent with Dr Marshall's colleague Dr Anil Dutta observing shoulder implant surgeries and techniques. The third week was spent with another of Dr Marshall's colleagues, Dr Raj Rajani observing the removal of tumours and pseudotumors associated with metal hip implants. The final week was spent in the laboratory with Dr Marshall where I taught her how to assay the periprosthetic tissue (removed after an implant fails) to look for cell death and DNA damage.

An introduction to Joint replacement:

Total Joint replacement (TJR) is a successful surgical intervention, eliminating pain, increasing mobility and restoring quality of life. Hip replacement is the most common joint replacement procedure comprising almost 80% of total joint surgeries \(^1\). There are several bearing material choices available (metal-on-polyethylene (MPE), metal-on-metal (MOM), metal-on-ceramic, ceramic-on-ceramic). Prostheses comprising an acetabular component of highly cross-linked UHMWPE (MPE) are the most frequently used worldwide. However, over a period of 10-15 years, a proportion (10-20%) will fail particularly in younger patients (<65 years old), who will often outlive the working life of the implant. This is generally due to patient specific factors, e.g., age at implantation, activity level \(^2, 3\), surgical technique, fixation of the implant to the bone, osteolysis and long-term bone remodelling, with 75% of
failures being attributable to aseptic loosening due to osteolysis. With conventional MPE, it is believed that the major cause of osteolysis and subsequent aseptic loosening is due to the biological response to UHMWPE wear debris generated at the articulating interface, mainly by the interaction of macrophages with these particles. Highly cross-linked UHMWPE offers significant advantages over conventional UHMWPE in terms of reduced osteolytic potential. However, failure does still occur in highly cross-linked UHMWPE, in particular there is an increase in rim fracture due to a decrease in fatigue resistance.

The size range of UHMWPE wear particles can vary from nanometers up to several millimetres. It is now clear that particles in the size range of 0.1-1 μm are the most biologically reactive. In addition to the size, the volume of wear debris plays an important role in the biological reactivity of the particles. The biological response to UHMWPE wear debris is dependent on the volume of particles within a critical size range. It has been found that only particle volume to cell number ratios of 10 μm³/cell are capable of eliciting a significant biological response to UHMWPE particles, in terms of osteolytic cytokine release. Analysis of periprosthetic tissues retrieved from revision surgeries has demonstrated the presence of biochemical mediators of inflammation that are associated with macrophage activation. Cytokines that have been detected in the periprosthetic tissues include TNF-α (tumor necrosis factor-alpha), IL-1β (interleukin 1β), and IL-6, IL-8, IL-11, macrophage-colony stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), transforming growth factor-α and -β (TGF-α, TGF-β) and prostaglandin E₂ (PGE₂). TNF-α is the most abundantly produced cytokine and has become a widely accepted marker for inflammation.
MOM bearings were once considered to be the future of modern joint replacement due to their low wear rates and improved strength \[^{[11]}\]. However, as the MOM bearing wears, metal ions are released into the local tissue and eventually make their way into the blood stream of the patient where they can travel; to distant sites in the body causing organ damage \[^{[12]}\]. Hypersensitivity reactions also occur with MOM bearings leading to significant tissue loss around the prosthesis and to the incidence of pseudotumours. It is now generally accepted that MOM prosthesis should be removed and replaced with either MPE or ceramic components.

**My Fellowship:**

On arriving in San Antonio on the Sunday evening I had to hit the ground running. 7am Monday morning I gave my first talk. I spoke to the entire orthopedic department, outlining my research ideas and explaining my fellowship. Then I did some paperwork, got my ID badge and was in the OR all before 9am!
Dr Marshall had really given some thought as to the different types of surgery I would get to scrub in on during my fellowship and I was extremely lucky to see a mixture of straightforward primary joint replacement surgeries and complex and challenging revision surgeries. My first case was a primary hip. Hip replacement surgery becomes necessary when the hip joint has been badly damaged (often from osteoarthritis) and the resulting pain cannot be satisfactorily controlled by analgesia. Dr Marshall carries out both anterior (front) and posterior (rear) approaches for primary hip replacement. Generally, slightly built or very active people are offered the anterior approach since it involves less damage to the abductor muscles. Less active or more heavily built people will have a posterior approach. This first case was a posterior approach, primary hip in a 62 year old female with advanced osteoarthritis. A, MPE prosthesis was selected. Dr Marshall does not use MOM implants and generally selects MPE prostheses unless the
patient is young and very active in which case a ceramic-on-polyethylene component would be used.

A posterior approach primary hip replacement.

My first exposure to hip revision surgery was a 70 year old male patient who required revision surgery due to pain and chronic dislocation. Lab results indicated that this patient’s pain was likely due to infection arising from the primary surgery. Revision surgeries are very different depending on the presence or absence of infection, amount of bone loss, abductor muscle strength etc. In this case, it was decided to remove both the femoral (ball joint) and acetabular (cup) components from the primary surgery. An antibiotic spacer was then added (bone cement impregnated with antibiotics). This spacer would stay in place for six to eight weeks to allow the infection to subside. Then the spacer would be removed and replaced with new hip replacement components.
An example of the femoral component of antibiotic spacer used to treat infection prior to revision surgery.

Dr Marshall also carries out primary and revision knee surgeries. My first exposure to a primary knee replacement was a 64 year old morbidly obese female with osteoarthritis in both knees. This patient had been on a weight loss program prior to surgery. With knees, if the patient is very obese then surgical access can be impaired resulting in less than perfect alignment and potential problems later on. 6 weeks after the first surgery, this patient was scheduled to have her other knee replaced.
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Primary knee replacement, opening up the knee.

Drilling the holes in order to fit the femoral component of a primary knee replacement.

That same day I scrubbed in on a complex knee revision surgery where the original implant needed to be revised due to fracture. This case was a 93 year old female who had simply knelt down from a chair and
fractured the femoral component of the knee replacement. The tibial component was also loose and therefore required replacement.

Fractured femoral component from knee replacement.
Primary knee replacements are minimally invasive to the femoral and tibial bone (A). Revision components are more invasive resulting in more bone loss (B). This patient needed a complex type of revision arthroplasty often used in cases of bone cancer (C).

A.  

B.  

C.  

*Primary and revision knee components.*

*Dr Bladen with patient after knee revision surgery.*
Dr Marshall and Dr Bladen during knee revision arthroplasty.

I was lucky enough to see a wide variety of primary and revision hip and knee surgeries but want to take this opportunity to highlight some of the more extraordinary cases.

I got to scrub in on a hip revision where the acetabulum (cup) had migrated into the pelvic cavity. The whole pelvis had to be reconstructed before a new acetabular component could be fitted.
Migration of acetabular component into pelvic cavity.

Opening up the hip ready for removal of damaged acetabulum and reconstruction of pelvis.
The acetabular shell (Smith and Nephew USA) used to reconstruct the acetabulum prior to fitting new acetabular component.

This was an extremely complex surgery and involved significant physiotherapy afterwards but this patient is now able to walk unaided.

Metal-on-metal (MOM) hip replacements can cause catastrophic bone and soft tissue damage. This case is a 54 year old male physician. He is an active cyclist and in 2006 was hit by a car whilst out on his bike resulting in a femoral fracture. The fracture was fixed but two years later he developed avascular necrosis (bone death) in his femoral head. He was given a MOM primary hip replacement by a surgeon in Dallas and came to Dr Marshall in July 2011 complaining of severe pain, chronic dislocation and a significant limp. Dr Marshall tested his metal ion levels and found that he had elevated levels suggesting that his MOM prosthesis was breaking down. X-ray indicated a well fixed prosthesis but MRI showed significant soft tissue loss in the area surrounding the metal components. Upon revision surgery, he was found to have significant necrosis of the soft tissue surrounding his hip and significant loss of abductor muscle tissue (causing him to dislocate). The dead tissue had to be completely removed and the metal components were replaced with a ceramic femoral head (active patient) and a polyethylene
acetabular cup. His abductor defect was then corrected using buttock muscle. Prior to me leaving Texas, this patient was back on his bike.

*MRI showing soft tissue loss around MOM components.*

*Opening up the hip – note the significant loss of abductor muscle.*
Necrotic (dead) soft tissue surrounding the MOM components.

Repair of damaged abductor muscles using buttock muscle.
I then spent a week with Dr Anil Dutta observing shoulder replacement surgeries. This is a very interesting and technically demanding procedure. I saw one conventional and one reverse (19 year old kid-trauma). I was surprised how delicate these procedures were in comparison with hip and knee surgeries, due in part to the smaller size and complex vasculature of the upper arm and shoulder. Dr Dutta didn’t allow me to take as many photographs as Dr Marshall but the science behind the implants is much the same as hip replacement. Wear and wear debris is not as big an issue in shoulder replacements simply because the shoulder is not a load bearing joint the way the hip is. MPE components are used most frequently with a polyethylene cup (glenoid) and a metal humeral head or the reverse.
I then spent a fascinating week with Dr Raj Rajani (orthopaedic oncologist) observing tumour resections and amputations. The amputations were quite harrowing especially one patient who was only 28 years old and had a long history of osteosarcoma. He had been through many different surgeries including removal of some of his femur and most of his tibia followed by specialist revision arthroplasty so that he could walk. Unfortunately his tumour was particularly aggressive resulting in him having an above knee, mid thigh amputation. His prognosis is poor and he is likely to die in the next 12 to 24 months. Out of respect for this patient I have not included and images of his amputation.

I also got to see how different surgeons often need to work together to solve complex cases. An example was a 62 year old male patient with metastatic osteosarcoma. He had tumour masses in the majority of his left leg above and including the knee joint. He had further tumour masses in his groin, abdomen and up his left side under his arm. This surgery was carried out in three stages over 9 hours. Firstly, Dr Rajani removed the cancerous bone and tissue from his leg before assisting Dr Marshall in fitting a specialist total knee replacement. Then urology surgeon Dr Catravas, removed the tumour mass from his groin along with one of his testicles. Finally, general surgeon Dr Hahn removed the abdominal tumour mass. This was a grueling but fascinating surgery. I was actually surprised to hear that this patient had an excellent prognosis. It’s incredible that we can overcome such significant surgery.

My final week was spent with Dr Marshall both in the lab and in surgery. We developed a method for assaying the periprosthetic tissue (tissue surrounding the implant) for hxpoxia (lack of oxygen), oxidative stress
and DNA-damage induced cell death. Dr Marshall and I have set up a tissue transfer agreement which will allow me to access tissue from all her patients in order to set up a research program for determining how different bearing materials damage their surrounding tissues. We are particularly interested in comparing MOM versus MPE bearings. We have already seen that both materials can cause hypoxia and oxidative stress but that DNA damage is elevated in MOM cases only not MPE cases. Our focus, therefore is to understand the mechanisms by which polyethylene causes hypoxia and oxidative stress in addition to further understanding the way in which polyethylene induces chronic inflammation in its surrounding tissues.

**Outreach:**

The main beneficiaries of this research will be the NHS and ultimately the patients who will receive more appropriately selected hip prostheses. This research will also benefit the UK prosthesis manufacturing industry. The results of this collaboration will be disseminated through presentations at national and international conferences (specifically the British Orthopaedic Society [BORS], and the International Orthopaedic Society [ORS]). Results will be disseminated directly to the collaborators, and a wider audience of academics and industry specialists through inclusion in the University of Leeds Institute of Medical and Biological Engineering [IMBE] research group annual report.
It wasn’t all work:

Now when Dr Marshall suggested we take a trip out on her boat I didn’t realise that what she actually had planned was to pull me behind it on a blow up rubber ring!!!! Of course me being me …I loved it!

We also took a trip to the Alamo.
References:
