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REVIEW ARTICLE

Anatomists and Geometers: 16th Samuel Haughton Lecture of the Royal Academy of Medicine in Ireland

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Abstract This paper is concerned with the interactions between medics and biologists on the one hand, the 'anatomists' of the title, and 'geometers', or engineers and physicists, on the other. It was delivered as the 16th annual Samuel Haughton Lecture on 23rd January 2010 at the *Bioengineering in Ireland* conference in Malahide. The paper begins with Samuel Haughton, the father of Irish biomechanics, and then discusses how anatomists and geometers have cooperated to solve problems in the areas of bone adaptation, fatigue microdamage, osteoporosis, third-level education and even art.

Keywords Samuel Haughton · Bone · Adaptation · Remodelling · Microdamage · Osteoporosis · Education · On-line teaching · Art · Anatomy

Samuel Haughton

Mathematician, geologist, cleric, medic, zoologist, bioengineer—Samuel Haughton is perhaps the closest we have come in Ireland to a renaissance man. Born in Carlow in 1821, he studied mathematics at Trinity College Dublin and graduated with the gold medal in 1843 [1]. The following year he was made a Fellow of the College and so was obliged to be ordained as a priest of the Church of Ireland. Membership of the Royal Irish Academy, Fellowship of the Royal Society and the Chair of Geology followed [2]. His interest in fossils led him to enrol as a medical student to study anatomy, and he subsequently reformed the Medical School and was involved in setting up the School of Engineering in Trinity [3].

Haughton was elected to the Council of the Royal Zoological Society of Ireland in 1860 and, when they died, dissected its animals from Bengal tigers to Australian cassowaries [4]. He is remembered in the Haughton House in Dublin Zoo, opened in 1898. He was a pioneer author on the geology of the Arctic Archipelago, and the meteorite impact crater in Devon Island, Canada was also named in his honour [5]. Its rocky polar desert setting, geological features and biology offer unique insights into the possible evolution of Mars, and so it is the site for research and training on the NASA Mars project. The crater is drained by the Haughton River which, by happy coincidence, flows into Thomas Lee Inlet (Fig. 1). He was Vice President of Dublin University Rowing club and calculated the work done in propelling an eight-oared outrigger at the rate of 1 knot—4 ft tons per man per minute [6]. He also showed that the 'shock of a ton dropped through one foot is just sufficient to fracture the anterior articulating surfaces of the second vertebra at their contact with the atlas, and that this fracture allows the shock to fall upon the *medulla oblongata*, so as to produce instantaneous death'. The formula he provided gave the length of the 'long drop' in feet, based on the weight of the 'patient' in pounds, so as to avoid 'clumsy' or 'painful' executions [7].

Yet, Samuel Haughton's career was not without controversy. Based on Rosetti's Law of cooling, Haughton miscalculated the age of the earth to be only 153 million years [2]. This did not allow enough time for natural selection to optimise the body according to his principle of least action, whereby the work to be done is effected by

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Fig. 1 The Haughton River, Devon Island, Canada, flowing from the Haughton Crater into Thomas Lee Inlet

means of the existing arrangements of the muscles, bones and joints, with any alteration being a positive disadvantage to the animal. Haughton therefore explained the similarity of muscles and bones in the vertebrate animals without making use of Darwin's hypothesis of descent from a common ancestor and concluded that it was all foreseen and that evolution itself was presided over by a divine Contriving Mind [8]. Haughton, the polymath, engaged in a lively correspondence with Charles Darwin who wrote 'I grieve that our theoretical views about the organic world differ so widely' [1]. McDowell and Webb [9] suggest that his deviousness in pushing innumerable schemes through College committees caused the future Provost George Salmon to remark 'Excellent! Excellent! You can just hear the lies trickling out of his mouth!' when he first saw the portrait of Haughton by Sarah Purser (Fig. 2).

Haughton's mathematical background and extensive dissections of a wide variety of animals, from humans to hippos, led to the publication of his major work *Principles of Animal Mechanics*. In the preface to the second edition, he wrote 'The observations and calculations contained in this book, have occupied my leisure hours for the past ten years and are now offered to the public with a view of showing the mutual advantages obtainable by Anatomists and Geometers from a combination of the Sciences which they cultivate. Anatomists will gain by the increased precision which numerical statements must give their observations and Geometers will find in anatomy a new field of problems opened out to their investigation.' [7].

This vision of combining the sciences led to the formation of the Section of Bioengineering in 1994 [10] and the establishment of the Samuel Haughton Lecture in 1995 (Table 1), for which the Royal Academy of Medicine in Ireland has awarded its silver medal since 1999 [11, 12].

Fig. 2 *Samuel Haughton* by Sarah Purser RHA, 1883, oil on canvas (reproduced with kind permission from the Board of Trinity College Dublin)

Table 1 Samuel Haughton lecturers, 1995–2010

1995 James Sheehan	2003 R. McNeil Alexander
Blackrock Clinic, Dublin	*University of Leeds*
1996 John O'Connor	2004 Neville Hogan
University of Oxford	*Massachusetts Institute of Technology*
1997 Pierce Grace [13]	2005 Alexander Blayney
University of Limerick	*Mater Hospital, Dublin*
1998 Annraoi de Paor [14]	2006 David Taylor [18]
University College Dublin	*Trinity College, Dublin*
1999 Michael Stephens [15]	2007 David Beverland
Mater Hospital Dublin	*Musgrave Park Hospital, Belfast*
2000 Tony Keaveny	2008 Patrick Prendergast [8]
University of California, Berkeley	*Trinity College, Dublin*
2001 Moira O'Brien [16]	2009 Frank Gannon
Trinity College, Dublin	*Science Foundation Ireland*
2002 John Orr [17]	2010 Clive Lee
Queen's University of Belfast	*Royal College of Surgeons in Ireland*

Osteology

Since joining the Royal College of Surgeons in Ireland over 20 years ago, I have had the pleasure of working with many anatomists and geometers [19], and would like to share with you five lessons which I have learned. The first

is an osteology lesson and concerns one of the things about which Haughton was sceptical—alteration. Increased loading of weightlifters' femurs, the pitching arms of baseball players and the racquet arms of tennis players causes the bone to alter by forming new bone. Decreased loading due to bed rest, plaster casts, space travel or around implants causes bone to be lost by resorption, so it becomes weaker, and the implants become loose. This interaction of form and function was codified by Julius Wolff [20] in 1892 as the *Law of Bone Remodelling* whereby alterations of the internal architecture and external form occur as a consequence of changes in the stresses applied to the bone according to mathematical laws.

To understand this, we need first to consider the cells involved. Osteoblasts are the builder cells. Cuboidal in shape, they sit on the surface and each day can make up to 1 μm of organic matrix, or osteoid, which is then mineralised to form bone. In doing so, 10–20% of the osteoblasts surround themselves with matrix and go into semi-retirement as osteocytes, lying in gaps in the matrix and communicating with each other via cell processes. In contrast, the osteoclasts are ten times larger and remove bone, first by secreting acid to demineralise it, and then by secreting an enzyme, collagenase, to resorb it.

We looked at underload by suspending a rat by the tail, as recommended by NASA, and looking at how its genes responded, how the bone changed shape and how its mechanical strength, measured by a twisting or torsion test, was altered. We found that underloading altered expression of two genes—c-fos and osteocalcin—and reduced bone formation, stiffness and torque strength when compared with normal, control rats [21].

We chose the sheep to look at overloading as the ulna acts as a strut to support the radius. When we removed this strut, strain gauges on the radius showed that surface strains increased by up to four times. Six months later, there was no difference in surface strains. By looking at cross-sections of the bones, we saw that the radius had adapted by getting fatter. Epifluorescence microscopy showed that new bone had been formed at the outer or periosteal surface, and the new mineral was labelled with fluorochrome dyes (Fig. 3) which the sheep had received intravenously [22]. We then looked at the original radius and found that microcracks appeared in it when overloaded, peaking at 6 weeks, but these then decreased and new, fluorescently labelled, osteons appeared instead, peaking at 10 weeks. This is explained by resorption of damaged bone by osteoclasts followed by formation of new, labelled bone by osteoblasts. So, overloading caused increased surface strains and periosteal modelling, with more microcracks and increased remodelling in the radius [23]. These anatomical data supported the first-order continuum damage mechanics model developed by our

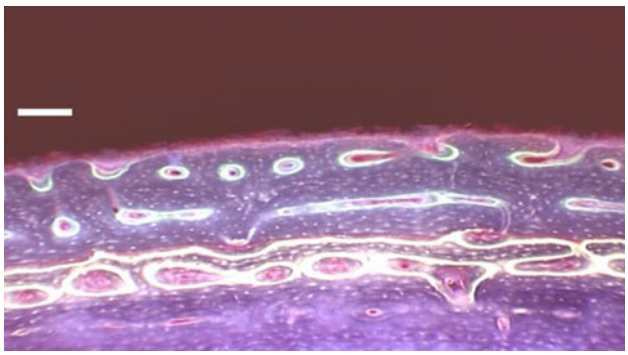

Fig. 3 New periosteal bone growth, labelled with fluorochrome dyes

engineering colleagues, Patrick Prendergast and David Taylor [24], who had proposed that the rate of new bone formation was determined by the rates of damage formation and repair.

Since then, theoretical speculation and experimental data have resulted in our 'Scissors Model' of bone adaptation, whereby osteocytes act as a mechanosensor, microcracks cut their cell processes, and this releases a chemical signal—RANKL. We have observed intact and ruptured osteocyte cell processes in microcracks, using scanning electron microscopy, and have used antibody staining to show a crack shearing cell processes as it grows [25].

RANKL attracts osteoclasts which demineralise and remove bone. Using cultured osteocyte-like cells, we have found that damage to their cell processes causes a proportionate increase in RANKL production and that this occurs in the absence of other proposed stimuli, such as cyclic strain or fluid flow [26]. This has nearly closed the loop on our *Nature Materials* model: repetitive loading causes fatigue microdamage, which shears osteocyte cell processes, which release RANKL, which activates osteoclasts, which resorb bone, which releases TGF beta, which stimulates osteoblasts, which repair the defect by laying down new bone [27]. So, bone is a self-repairing material; we now know how it adapts, and we can predict its behaviour mathematically.

Microdamage

A Fulbright Scholarship enabled me to work at the Orthopaedic Biomechanics Laboratory at Harvard and learn a second lesson about microdamage. As we have seen, microdamage is a stimulus for bone remodelling, but it is also an important factor in stress fractures in athletes and army recruits and fragility fractures in elderly patients. X-rays, scanning electron, reflected light and acoustic emission microscopy have all been used to detect

microdamage, but the gold standard method was basic fuchsin staining of cracks using transmitted light microscopy. However, microcracks are still difficult to find. We noted that basic fuchsin is composed of rosanilin and pararosanilin dyes, both of which fluoresce. They have large conjugated systems with electrons which, according to Stokes' Law, can be promoted to higher energy orbitals by absorbing excitation energy from incident light and then fluorescing, emitting light of a longer wavelength and different colour, as they return to more stable orbitals near the nucleus. Using UV incident light, the bone autofluoresces blue and the fuchsin in the crack fluoresces violet, but it is even easier to see the crack using green incident light when the fuchsin fluoresces orange against a darkfield [28].

However, fuchsin is not site specific as it can neither bind to the mineralised matrix in the wall of a crack, nor can it be used as part of a sequence—with toluidine blue for example—to label crack growth. So, we thought of the group of fluorochrome dyes we had used earlier to label new bone formation in sheep. First of all, we showed that all five of them—calcein blue, calcein, alizarin, xylenol orange and oxytetracycline—were as good as fuchsin at labelling microcracks and then we used them in sequence. We made a dumbbell specimen of bone and fatigue loaded it in compression in an Instron machine to generate cracks, with a bath of dye surrounding the specimen to label them. Calcein blue was put in the bath for the first three quarters of the test, and xylenol orange for the last quarter, and we were able to show a crack growing—labelled blue at first and then orange (Fig. 4) [29]. So, for the first time, we were able to measure both changes in mechanical properties and crack propagation in bone and show how one caused the other.

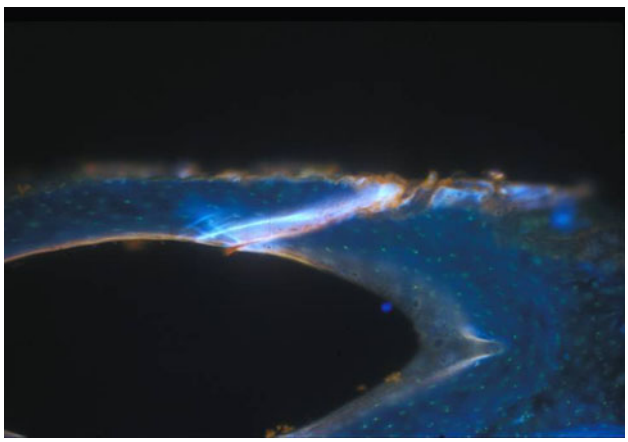

Fig. 4 Sequential labelling of microcracks in bone—*light blue* labelled with calcein blue in the first 75% of the fatigue test and an oblique, *orange* microcrack labelled with xylenol orange during the final 25% of the test

The method was still crude, however. Back in Ireland, we first used basic fuchsin and laser scanning confocal microscopy to show the 3D elliptical shape of a microcrack [30], which confirmed our earlier, theoretical predictions [31]. We then optimised the sequence and concentration of the fluorochrome dyes with ion chromatography and used them, first on scratches and then on growing cracks [32]. We then applied them in a fatigue test and showed a sigmoid, or S shaped, curve as cracks formed easily at first, then hardly at all and then rapidly to cause fracture failure [33]. This behaviour is typical of a fibre-reinforced composite material, and part of the reason for the flat part of the curve is that cracks interact with the microstructure of the bone, some being stopped while others are deflected around osteonal cement lines. These data gave rise to another theoretical model of the fatigue behaviour of bone, where the crack growth rate is dependent on the stress intensity, microstructural barrier spacing and crack length. We used this model to simulate living bone under stress and showed that, as in real life, it will initially do nothing, then adapt and finally fracture when subjected to increasing loads [34].

We have also worked with Thorri Gunnlaugsson [35, 36] and his group of chemists to develop a delayed-action fluorescent dye, so that the crack still shines even after the background bone has gone dull, which makes histological detection much easier and, potentially, machine readable. We looked at the damaged crystal lattice of the crack walls and developed an iodine-based agent which could chelate to calcium and be visible using non-invasive microCT [37]. Unfortunately, the radiation dose required is not suitable for clinical usage, so we are currently looking at agents that will enable us to count cracks using MRI. In summary, by labelling microcracks, we can quantify microdamage and develop models of the fatigue behaviour of bone which will help in the prediction and prevention of fractures.

Osteoporosis

Funded by PRTLI Cycle 3, the Bone for Life collaboration with the Trinity Centre for Bioengineering enabled the basic knowledge we had gained about bone remodelling and microcracks to be applied to a clinical problem—osteoporosis. The US National Institutes for Health defines osteoporosis as a skeletal disorder characterised by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the integration of two main features: bone quantity, usually measured as density, and bone quality. The statistics are sobering (Table 2).

We used ovariectomised sheep as our model as they are similar to post-menopausal women in terms of hormonal

Table 2 Osteoporosis statistics

1. 1 in 3 women and 1 in 12 men in Ireland will have osteoporosis after the age of 50 years
2. Every 3 min someone has a fracture due to osteoporosis: vertebral > hip > Colles
3. The fiscal cost is €17 billion annually in Europe
4. Hip fractures worldwide: increasing from 1.7 million in 1990 to 6.3 million by 2050
5. Following hip fracture:
50% of patients are unable to walk without assistance
25% of patients cannot live independently
20% mortality within 6 months of fracture

balance, skeletal kinetics, bone remodelling and size. The flock was divided into Control and Ovariectomy (OVX) groups and studied at 12 and 31 months—along with a subgroup which was treated with a bisphosphonate drug that prevents bone remodelling. We showed that ovariectomy significantly increased remodelling and that bone resorption exceeded formation, so the bones became much more porous when seen using microCT (Fig. 5) [38].

When bone specimens were fatigue tested, we found that the density of microcracks did not differ significantly between Control and OVX groups, except at lengths greater than 300 μm when there were significantly fewer in the OVX group. The ability of microcracks to propagate depends on both crack length and bone microstructure. Most cracks were found in old, highly mineralised, interstitial bone and, while some long cracks penetrated old osteons, cracks of similar length did *not* penetrate the newer, labelled osteons. This shows that, while remodelling made the new bone more porous, the resultant loss of strength was partially compensated by the new osteons stopping crack growth and so improving its material properties [39]. A second compensatory mechanism is the alteration of the shape of the bone, which increases its structural strength [40]. In trabecular bone specimens, bone volume fraction was reduced in the OVX group due to fewer and thinner trabeculae, but was reversed by drug treatment. Not surprisingly, mechanical strength was reduced in the OVX group, and this too was reversed by drug treatment [41, 42].

There are limitations to this study—a supra-clinical dose of bisphosphonate was used, and our findings are only an indication of what happens in early stage osteoporosis [43]. However, we can say that both osteoporosis and its treatment greatly alter the mechanical behaviour of bone and its risk of fracture. The tendency for loss of bone mass to reduce mechanical strength is initially opposed by improvements in both mechanical and structural properties, but these effects are short lived, and would appear to have been superseded by the time osteopaenia or osteoporosis

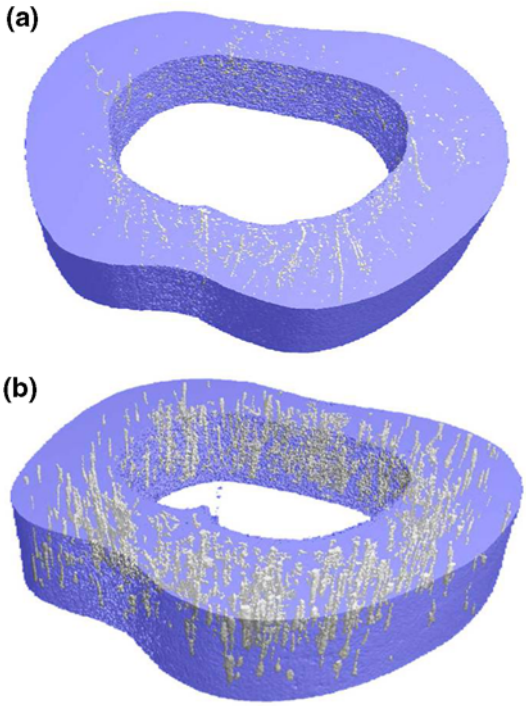

Fig. 5 Micro CT images from **a** Control and **b** Ovariectomy groups showing increased bone porosity

can be clinically diagnosed using current DEXA scans. It would be very helpful to be able to diagnose the disease earlier, and we are currently working on these, looking for early, serum markers.

Educate together

My fourth lesson was the importance of educating together. My time at Harvard was funded by a Fulbright Scholarship. Senator William Fulbright hoped that by educating people of different nationalities together it 'would bring a little more knowledge, a little more reason, and a little more compassion into world affairs and thereby to increase the chance that nations will learn at last to live in peace and friendship'. While they do not usually fight with each other, the same principle can be applied to anatomists and geometers. The Division of Health Sciences and Technology educates the engineers and physicists from MIT alongside the more research-oriented medics from Harvard Medical School and the results, as I saw at their silver jubilee celebrations, are most impressive.

We are making progress in Ireland. In 1998, the 4B7 Biomechanics course began in the Engineering School in Trinity and the All Ireland MSc in Biomedical Engineering, involving the universities of Dublin, Limerick and Ulster, UCD and RCSI has now been running for over a decade. For the past 2 years, the European Society for

Engineering and Medicine Summer School, based in the Trinity Centre for Bioengineering and the Department of Anatomy in RCSI, has taught engineering and medical undergraduates, while the Erasmus Mundus Masters Programme begins this year. The majority of participants have come from engineering backgrounds, and modules dealing with basic medical sciences have been included. These have been facilitated by the ready availability of textbooks in this area, many of which were specifically written for nursing anatomy and physiology programmes. In contrast, relatively few participants from medicine have taken up such courses to the detriment of scientific exchanges between engineers and medical doctors. The reasons for this imbalance are many and vary from country to country, but a consistent finding is the difficulty in taking the first step. 'Introductory' texts in bioengineering tend to involve vector integration early in Chapter 1. While in most countries entry to medical school is very competitive and requires high grades in mathematics, little more than arithmetic is required during the course itself, so numeracy undergoes disuse atrophy.

Furthermore, to paraphrase George Bernard Shaw, medics and engineers are separated by a common language. To the medic, stress and strain are both symptoms of anxiety, while to the engineer they are defined by equations and the symbols σ and ε. To the average medic this is, literally, all Greek. To address this problem, a new series of *First Step* papers has begun in *Technology and Health Care* aimed at medics to help bring them to the level where they can *begin* an MSc in biomedical engineering. Written by engineers who are leaders in their field, with input from medical colleagues, they cover the basic engineering *principle*s underpinning biomechanics, bioelectronics, medical informatics, biomaterials, tissue engineering, bioimaging and rehabilitation engineering, and include clinically relevant *examples*. These papers have recently been published as a book *Basic Engineering for Medics and Biologists* [44]. As Albert Einstein may have said 'Everything should be made as simple as possible, but not simpler'.

Artists, anatomist and geometers

I was invited to become the Honorary Professor of Anatomy in the Royal Hibernian Academy and so my fifth, and final, lesson is about art. Anatomists and geometers may be the subject of art (Fig. 6). This group portrait of the members of the RCSI Department of Anatomy and our students, painted by Robert Jackson, continues the long tradition of Anatomy Lesson paintings [45, 46]. Having been selected for the 2010 RHA Annual Exhibition, it now hangs in the room it depicts [47].

Faced with teaching anatomy to a large number, and diverse range, of students, we sought the help of geometers—Anil Kokaram and his Sigmedia Group from Electronic and Electrical Engineering in TCD. Dissections were filmed, edited and annotated and a system designed that would be both interactive and download in seconds [48]. This *Dissection Guide* is now used on-line by medical students in Dublin and Bahrain, by surgical trainees in Ireland and Oxford and by the Anatomical Society. It is used, as a DVD, by surgeons in the nine African countries—Ethiopia, Kenya, Malawi, Mozambique, Rwanda, Tanzania, Uganda, Zambia and Zimbabwe—that form the College of Surgeons of East, Central and Southern Africa. During the project, Anil went to Hollywood to be presented with an Oscar 'for the design and development of the Furnace integrated suite of software tools that robustly utilises temporal coherence for enhancing visual effects in motion picture sequences'. This software is clearly evident in films such as *The Matrix*, and his expertise explains why our *Dissection Guide* is simple enough for anatomists like myself to use.

Fig. 6 *The Anatomy Lesson of the Irish College of Surgeons* by Robert Jackson, 2009, oil on canvas (reproduced with kind permission from the Council of the Royal College of Surgeons in Ireland)

An SFI grant is enabling us to take this further and, together with the artist Mick O'Dea and the RHA School, we are currently working on 3D Surface Anatomy videos to teach medics, engineers and artists [49]. Anatomy may be applied by anatomists and geometers, but only by artists can it be transformed [50].

Conclusion

As Samuel Haughton predicted, I have gained greatly by combining anatomy with engineering. After 20 years of working with geometers [51]—and two with artists—I have learned that:

1. Bone repairs and adapts in ways that we can predict.
2. Microdamage can be quantified and fractures predicted and prevented.
3. In osteoporosis, there is a transient adaptation of mechanical and structural properties to offset the reduction in strength due to bone loss.
4. Engineers and medics should be educated together.
5. Anatomists and geometers can be creative.

I thank the President and Secretary of the Council of the Section of Bioengineering, Prof. Pierce Grace and Dr. Kevin O'Kelly for inviting me to give this 16th Samuel Haughton Lecture, and it is a pleasure to make the following acknowledgments.

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