Only One Link in the Chain of Destiny can be Handled at a Time

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I am, as some of you may know, fond of quotations. Particularly those of Churchill. In a Symposium which has 'Larger than Life' in its title, I think that it would be highly appropriate to lean heavily on the words of this great man. And since Churchill never ever used PowerPoint presentations to accompany his greatest speeches, in fact he had an absolute disdain of such technology, I decided that I would emulate him in this respect as well.

One of the most interesting aspects of the life of this speech maker was that wherever possible he would not use notes, and would practice in front of the proverbial mirror for hours to get the greatest effect, but he experienced one of his most embarrassing moments when, in a very important speech in his early career, he lost his place and train of thought and dried – up, and was forced to sit down, unfinished, ashamed and humiliated, in the very House of Commons he was later to dominate with his words. And so, to avoid this experience, and to pay my greatest respects to Buddy in a philosophical discourse on a subject of mutual interest, in which I dare not get a word wrong, I have decided to use a script to guide me through.

I have also taken Pat's enticement, if I may paraphrase him, to be controversial, expansive and forward looking, not being constrained by the normal etiquette of scientific presentations. After all we are here to honour Buddy, who is not normally constrained by etiquette.

What Churchill would have made of Buddy I am not so sure. He had the best insulting put-downs I have ever heard, but I know that he would never have included Buddy in the list of recipients of his library of acerbic comments. "An empty taxi drew up and out stepped Ratner". I think not.

Most of his memorable speeches were entirely irrelevant to science, or even to Buddy if it comes to that, although with respect to the latter I was tempted with the following:

I had been brought up and trained to have the utmost contempt for people who got drunk, and I would have liked to have the boozing scholars of the universities wheeled into line and properly chastised for their squalid misuse of what I must regard as a gift of the gods.

He said that in 1930 and of course he mellowed a little, well quite a lot really, saying later on that he had taken more out of alcohol than alcohol had taken out of him.

But I decided that one sentence from Churchill profoundly represents some of the opinions that I have been adopting in recent times:

It is a mistake to look too far ahead; only one link in the chain of destiny can be handled at a time.

Let me explain, and relate this sentence to the science of biocompatibility, a subject in which Buddy and I have had a common interest these last 35 or so years and in which we have struggled with the Churchillian concept of ***terminological inexactitude***. That is my theme today. How is the chain of destiny within biocompatibility going to be handled. And there are two aspects of this. The first is scientific and the second philosophical.

Biocompatibility is possibly what Churchill could have had in mind when he used the phrase;

It is a riddle wrapped in a mystery inside an enigma

although I suspect that the history books will tell us otherwise and that he was really talking about Russia.

To rephrase, however, biocompatibility is a material wrapped in a biology inside a host.

Churchill would often repeat the key sentences:

Biocompatibility is a material wrapped in a biology inside a host.

Hosts may be enigmatic, that is ambiguous or inexplicable, as in the name given to the electro-mechanical cipher engine used by the Germans in World War II against Churchill, which took a massive effort in the UK to decipher. I firmly believe that it is the enigmatic variations of the hosts, the patients, that is primarily responsible for uncertainties in biocompatibility, and probably always will be.

The biology is still a mystery, but a mystery is more solid than an enigma and is likely to be solved. The biology of biocompatibility is complex certainly and we are far from clear just how the various processes subsumed within the totality of biocompatibility control the overall mechanisms. But this is soluble, as the links in this particular chain of destiny are being handled both sequentially and concurrently.

Which leaves us with the material. Can a material be a riddle. Is not the material the stable starting point in biocompatibility, the cause of the effect, the well characterised, reproducible focus of attention. You don't get much when you put material and riddle together in Google, apart from a Mr Riddle who was apparently keen to show off his material, but we needn't go there. In reality the material is the riddle in biocompatibility because we still do not know which characteristics of the material, including its surface, control the biology. I will come back to this and dwell on it a little because this, after all, is Buddy's territory, and I will honour Pat's directive in so doing.

I would like to explore this by discussing a few clinical manifestations of biocompatibility phenomena so we can see where the enigmas, mysteries and riddles are in that chain. And here, at the very heart of this presentation, I would like to introduce you to the concept of metastable biocompatibility.

Let me start with a mechanical heart valve. The materials we currently use here include a form of carbon, a form of textile and a form of an alloy. Are these riddlesome. I suggest not and I further suggest that the biocompatibility of mechanical heart valves has nothing to do with the materials we use, provided that we keep to this framework of say, graphite, Dacron and cobalt-chromium. I do not know of one situation in which any characteristic of these materials has been the cause of any clinical bio-incompatibility.

The chain of destiny of these heart valves is directly related to the biology, which is concerned with the resistance to interference with the natural processes of wound healing and haemostasis, these processes being fairly well understood. It is possible of course for mechanical heart valves to fail through a variety of what might be considered as adverse biological responses, including thrombotic occlusion, thrombo-embolic events, paravalvular leakage, pannus overgrowth, haemolytic anaemia and endocarditis. I will leave the latter one alone for the moment since bacteria get in the way of these mechanisms, so to speak.

As far as I am aware, the processes which control these biological phenomena are influenced by clinical technique, which is important for the regulation of the healing phase, and the design and related haemodynamic characteristics of the valve, which largely control susceptibility to initiation of unacceptable interactions with cellular and proteinaceous components of the blood. I regard the biology here as being reasonably well defined.

With one caveat. And that is the host enigma. Many times I have been asked to defend heart valve manufacturers in legal proceedings concerned with adverse events, particularly thrombosis. We all know that prosthetic heart valves are associated with a predilection to cause thrombosis and we have known ever since the first valves were used that it is possible to manage this risk by the use of anticoagulants. Every time I have looked at the medical records of the individual patients involved in such a case, who have suffered from some occluding thrombus or thrombo-embolic event, there has been clear evidence of sub-therapeutic anti-coagulation. A very recent case in the UK where the patient suffered a fatal occlusion at 10 weeks, the INR values over the first couple of weeks were routinely below 1.5 and oscillated over the subsequent weeks around the 2 mark and it was of no surprise that a fairly well organised thrombus was found to be partially occluding the valve at post mortem. This happens time and time again.

It is patient variability. The crucial link in the chain of destiny of these valves is the enigmatic patient compliance. The stability of the patient's life is controlled by it. This phenomenon may be seen as host dependant metastable biocompatibility. As is usually the case, metastability has well defined mechanistic origins but the timing and precise circumstances of the occurrence of the transformation change are usually unpredictable. The formation of the thrombus is not a linear continuous process. The links in the chain may be obfuscated by random events.

The situation with intravascular stents is a little different but follows a similar pattern. I was very interested to see on the way here from Singapore on Wednesday my theme being played out with a whole page advertisement of Boston Scientific in USA Today under the banner headline 'We answered every question Frank Kemp had about drug eluting stents – we'd like to do the same for you'. Being a Brit, I have no idea who Frank Kemp is, but I figured Boston Scientific must have thought it an important issue to pay for a whole page advert. Parenthetically it is unfortunate when biocompatibility is discussed in such a negative context in the media.

I suggest to you that the treatment of atherosclerosis and the performance of and experiences with these stents provides a microcosm of biocompatibility mechanisms and metastability. Angioplasty itself is a powerful technique for ameliorating the clinical influence of plaque but, as we all know, the inevitable irritation of the endothelium, and also of the underlying smooth muscle cells, provokes proliferation and intimal hyperplasia such that some degree of re-stenosis is almost inevitable. The chain of destiny post-angioplasty without some other intervention is actually quite predictable.

But now we do intervene with a medical device and a biomaterial. To overcome the effects of the irritation to the endothelium caused by angioplasty, we carefully place a metallic stent at the site of the lesion and, through controlled expansion of the said stent, we carefully hold the blood vessel open mechanically. Or to put it more crudely, we squash, or I think you might say, squish, a foreign object in the shape of a metallic frame into that very sensitive endothelium.

What happens next I don't think has anything to do with biocompatibility. In spite of some claims to the contrary, the consequences of stenting have nothing to do with the material per se but all to do with the biology of the blood vessel wall. The vascular endothelium, intrinsically being a metastable structure, is influenced in all of us ageing folk by both innate and acquired characteristics, blood pressure and cholesterol for example, and in-stent re-stenosis is almost inevitable. It will not matter whether the stent is stainless steel, cobalt chromium or Nitinol.

And so we intervene again, this time with a solution to the problem we have just introduced. Having just stimulated the endothelium into proliferation, let us counteract that with an anti-proliferation policy, typically with a drug eluting stent, presenting to the tissues a minute amount of a chemotherapeutic or anti-proliferative drug. This is exquisite

metastability, holding the material – tissue interactions in check, possibly until something happens within the biology to upset the equilibrium. Biology – dependant metastable biocompatibility. And what Boston were trying to explain was that in a very small number of patients, this equilibrium has been upset, not through recourse to endothelial proliferation but to thrombosis, the late thrombosis of intravascular stents. The metastability of biocompatibility is often a tease.

Let me move on now to total joint replacement procedures, where metastablity abounds.

In fact, classical materials science metastability became a serious issue in total hips a few years ago in the case of the yttria stabilised transformation toughened zirconia femoral heads. These components had acquired quite a good reputation because of their generally superior fracture toughness compared to other oxide ceramics such as alumina but their performance was predicated on the presence of a metastable triclinic phase which would transform spontaneously in the strain field at a crack tip, slowing down the crack and giving the enhanced toughness. However, a change to the production process by the sole supplier of zirconia femoral heads to the world's orthopaedic manufacturers, altered the metastability during a heat treatment producing far inferior mechanical properties and catastrophic clinical performance.

I have also been involved in some interesting situations that are developing in the new generation of metal – on – metal hip replacements, where small numbers of patients also suffer catastrophic failures through massive inflammatory reactions over the first year or so. I cannot present you with the evidence here to day since the analysis is incomplete but I have been quite struck by similarity with the circumstances found in some other metallurgical phenomena involving what is being described as metastable corrosion, since here we have strongly passivated alloys that electrochemically should be considered stable under physiological conditions, but where the combination of galvanic, fretting and crevice conditions lead to initially localised focal points of instability which are able to coalesce and propagate to quite massive corrosion pits, which lead to profound inflammatory responses. This is material – based metastable biocompatibility.

The issues of metastability in joint replacements are even more generic than that. I would like to include here a literary analogy. Niall Williams, regrettably not a cousin of mine, but, to the delight of Peggy, a master of

the Irish tale, wrote the following in his book 'The Fall of Light', which I recommend profoundly to all connoisseurs of modern Irish literature.

I am going to paraphrase a little bit, as we Celts are allowed to do with each other, but of course without recourse to plagiarism. In the following, please translate the Celtic ***'gypsy'*** into the Andersonian language of inflammatory cells, let us say, for the sake of argument, the big Mac, and translate the ***'new country'*** into the peri-prosthetic environment of the hip replacement.

Some orphaned young Irish brothers, for which read particles released from their parent with no recourse to going home, having escaped the law, became lost in their anxiety to get away and were being swept along in the fast flowing Shannon, or slow flowing but not yet stagnant peri-prosthetic fluid, and were encountered by these gypsies;

The gypsies had travelled south in the dying of the year, through the secret ports that were used by spies, -

or in our language by receptors.

They had travelled to this country not from need nor flight but simply because it was there, because it was marked on the outer edge of maps and looked the splintered part of some greater whole, and because they could not be still.

That is to say, the macrophage, perfectly honed to establish contact with and destroy invading bacteria, recognises the presence, at the periphery of perception, of some splintered particles, and cannot stand still.

Nothing living stood still, and in their travels they had seen the variety of the world and accumulated its slow wisdom.

A basis of immunity if there ever was one.

Some of them had journeyed around the perimeter of the shore and then left once more. Others, drawn by the green mesmerism of the land, voyaged around it in covered caravans. They took to its crooked roads, and found the circuitous routes that defied the usual measurement of progress to be an apt landscape for gypsies. These were roads that went nowhere, along which they lost all sense of time. Their lives, which had once been measured by the new places they discovered, now took on the dimension of a long somnambulant dream. They were

accustomed to seamless time, and rode their ragged caravans on through it, content in the simplicity of such living. Close to the shoreline that morning, the brothers passed mostly submerged, and they were taken up from the river by the gypsies. While the brothers lay there, the women watched them to see the shape of their dreams and the men gathered and spoke excitedly of the catch the river had yielded.

Imagine, itinerant monocytes from the central circulatory system transforming into macrophages and quietly infiltrating the capsular tissue, just like itinerant Romanies from the central European system invading the capsular fringes of Ireland, wandering around, apparently aimlessly, but exquisitely attuned to the plaintiff signals from young released familial fragments and engulfing them in well rehearsed manoeuvres. We can imagine the occasional itinerant polyethylene particle being taken up thus.

But the story does not stop there and I now revert back to my own Celtic origins, and by that I mean real Celtic with a 'c' and not Bostonian seltic with an 's'. Had those particles been anything other than Celtic in origin, they would have been subsumed, consumed and ultimately buried in the lymphatic cemeteries of humanity. But resistant, often foolish, buggers that they are, the Irish fight back and these young red haired brothers return from the phagocytosed dead, and steal the gypsies horses, no surprise there, and then their women, almost up to the standards of their Welsh kinsmen, and all hell is let loose. The gypsies turn on them and inform the Garda of all people, the T for terror of all lymphocytic defenders of the state, and then they signal their erstwhile enemies, the bone crunching, osteolytic cousins to take up the action. And more than hell, all prostheses are now let loose.

We all know that stability has not been the hallmark of Ireland these last few centuries, and this analogy leads us to metastability and instability. What we have in the complexity of total joints, where I and a few other people in this room now have a vested interest, is a combined material / biology / host - based metastable biocompatibility phenomenon. Provided we follow what are now considered as fairly well grounded basic conditions, our devices should outlast the patient. But metastability can intervene at any time. The links in the chains of destiny of these outstandingly successful medical devices should be straightforward, but often the weakest link comes as a surprise.

Earlier I said I would look at the quotation from both scientific and philosophical perspectives. Moving to the latter just briefly, there are

some areas of science and technology, perhaps even most areas, where progress is continuous. Developments follow on from one to the other, explicably, rationally, even incrementally, where the links are discrete and provide a logical progression. Most of metallurgy, where I came from, was a logical progressive science, as developments in thermodynamics, crystallography, alloy structures and phase diagrams and deformation theory led to ever improving mechanical properties over wide-ranging environmental conditions. All very good, indeed extremely good, science, but the links were always visible and the next goals readily identifiable. Even superconducting alloys and nanocrystalline metals were logical extensions to existing paradigms.

There are other areas of science where developments may be considered discontinuous, or indeed where the phenomena are themselves discontinuous. And by that I mean that the logical progression of a science may suddenly take a sharp turn in what was hitherto an entirely unexpected direction and where the future path could not have been predicted until the pivotal invention or discovery that caused that turn took place. This is where the one link in the chain of destiny becomes hugely important.

I have to admit that there are many areas of science where it might seem that such a discontinuity has occurred but whereas, in fact, it had been predicted long before but just never achieved, or not achieved in a useful way. Cloning is an example, for although cloning from adult cells came to significance in 1996 with Dolly, the word itself was first used by Haldane in 1963, the first nuclear transfer experiments were carried out back in 1928 and tadpoles were cloned in 1952.

I do not have time today to explore this theme but I often think that in science it is difficult to predict the future because it is so often discontinuous, where it is impossible to see the future links of the chain because that one crucial discovery, or invention, or concept, has not yet occurred. I now have a clear personal view of the biocompatibility of long term implantable devices, which I discussed in debate with Buddy at last years Gordon Conference, which is based on stable inertness. I am sure, however, that future links in the chain of biocompatibility will lead in different directions, in perhaps tissue engineering and biotechnological directions, where we have to start all over again.

As scientists we have to be careful here because we do not usually have the same gifts as politicians, described by Churchill -

As having the ability to foretell what is going to happen tomorrow, next week, next month, next year, and to have the ability afterwards to explain why it didn't happen.

As he also said;

We occasionally stumble over the truth, but most pick themselves up and hurry off as if nothing had ever happened.

I would like to congratulate Buddy on his efforts over these last 35 or so years to recognise the truths in biocompatibility and avoid the temptation to hurry off into wrong directions. Whether he has succeeded in the latter will of course be revealed tonight in the Roast and I will reserve further comment until then.

In closing I have to put on record my thanks to Peggy, who most of you will know, and who not only bought me a few years ago the first edition copies of Churchill's books and speeches which have been a magnificent inspiration, but also put me right about the real Irish, the Bostonian Irish, and most else I have learnt outside of Liverpool in the last decade or so – no metastability there, but as Buddy and Cheryl will know, just true biocompatibility.