

Do Not Go Gentle Into That Good Night

Text of speech given to the TERMIS-EU Chapter meeting in Rhodes, Greece, 30th May, 2019

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Preamble

This text provides the verbatim transcript of the speech given by David Williams after he was presented with the Chair's Life Achievement and Contributions Award of TERMIS-EU at their meeting in Greece in May 2019. During the presentation, Professor Williams mentioned several of his publications that provide the background to his points about biocompatibility myths; these are (a) Williams DF "Essential Biomaterials Science", Cambridge University Press, 2014, (b) Williams DF On the mechanisms of biocompatibility, Biomaterials, 2008, 29(20), 2941-53, (c) Williams DF On the nature of biomaterials, Biomaterials, 2009, 30(30), 5897-909, (d) Williams DF The biomaterials conundrum in tissue engineering, Tissue Engineering Part A, 2014, 20 (7-8,), 1129-31, (e) Williams D F There is no such thing as a biocompatible material, Biomaterials, 2014, 35(38), 10009-14. (f) Williams DF Biocompatibility pathways: Biomaterials-induced sterile inflammation, mechanotransduction and principles of biocompatibility control, ACS Biomaterials Science and Engineering, 2017, 3(1), 2-35, (g) Williams DF Biocompatibility in clinical practice: predictable and unpredictable outcomes, Progress in Biomedical Engineering, Inst Physics (UK), 2019, 1, In Press, (h) Williams DF Biomaterials for sustainable tissue engineering, Frontiers in Bioengineering and Biotechnology: Tissue Engineering and Regenerative Medicine. 2019 In Press.

Heinz, Maria and especially Dimitrios, I thank you for the opportunity to return to Greece; I came to Greece for the first time over 50 years ago, in 1966, when, as a student, I spent time in Peloponnesia, and watched a remarkable, epic, production in the amphitheater in Epidavros. Tonight I hope I can bring a little Greek and Welsh theatre to this meeting, after a long day of sessions and before the soiree.

**Do not go gentle into that good night
Old age should burn and rave at close of day
Rage, rage, against the dying of the light**

So wrote Dylan Thomas, desolate at the sight of his father going quietly in his last days, in contrast to the rest of his boisterous life. Rage, rage, Dylan suggests.

On the other hand, the boisterous archbishop of Cape Town, Nobel laureate Desmond Tutu, gives different advice after finding people did not listen to him about apartheid in South Africa:

Do not raise your voice, improve your arguments

Ladies and gentlemen, I wish to show you tonight that you should not go gentle, but you need good arguments delivered in a quiet measured voice for people to listen.

This award comes with the adjectives 'Chair', 'Life', 'Achievement' and 'Contribution'

I really appreciate this honor, and the implications of these descriptors.

An award that is prefaced by "Chair" sounds dignified, as with some appointments you may get in Asian universities, near the close of that day, of Chair Professor, which has the edge over "honorary", "visiting" or "adjunct". None of us realized at the time, however, that there was an even greater significance to the 'chair' award, since I have been actually awarded a chair to sit on, caused not by old age as with Dylan's father, but rather to help with my recovery after spinal surgery a few months ago; we thought that standing for half-an-hour was not a good option.

For achievement and contribution, I would make no claim myself but if TERMIS-EU considers that I have made noteworthy contributions I will gladly and humbly accept their verdict. During those contributions, of course, I have made mistakes, and I will refer to some of these this evening.

But life, or lifetime, I am not so sure. A lifetime is a duration of existence, which implies that this talk I give tonight signals the end of that existence, which is not so. Awards at or towards the end of life or career represent a difficult balance. Nobel prizes cannot be given posthumously but committees usually try to avoid embarrassment by waiting until potential recipients are no longer likely to disgrace themselves before they die, although we know that doesn't always work by the example of James Watson who was still pronouncing his racist views into his 90s.

So I accept this award in the spirit that was intended, and inform you now that, although you may not see me so often, you will still hear me, and perhaps more vociferously so, hopefully to the benefit of biomaterials science and regenerative medicine.

As some of you know, I have added the writing of poetry to my portfolio recently. Two years ago after a series of deaths of iconic music makers, including Chuck Berry, Leonard Cohen, George Michael, Hugh Masekela and Aretha Franklin, I wrote a poem that I called "The Passing of the Masters" and included the phrase

"The rock face that separates the alluvial plain of ordinariness from the peaks of achievement is sheer".

For most of us, we live in that alluvial plain and can only aspire to climb that rock face.

If I have a message to younger scientists and clinicians here tonight it is that the rock face is always there, and indeed seems more treacherous as days go by. It will always be an incredible

challenge, but never give up hope that you can achieve your own form of greatness – and I still live in that hope.

Peggy, my wife, who is here tonight and whom many of you know, years ago gave me a framed picture, recognizing my previous rugby-playing days, showing men, just like me who operated in the front row of the scrum, fighting for an oval ball, seemingly without hope, but with the inscription

“Champions get up, even when they can’t”

And talking of Champions, Geoff Richards and I were able to celebrate Welsh victory in this king of the sports this year, which was truly inspirational, but with due deference to my friends from Galway and Dublin, I will say no more about it tonight.

Now I have been speaking for five minutes and you will notice that I haven’t shown any slides.

Nor will I

It is not that I don’t have any slides, but they are unnecessary and probably distracting from tonight’s messages. I have spoken without slides before. I once heard someone say

“I heard David Williams, with no slides, and it was quite good”

Only to be followed by the dispiriting comment from someone else

“I saw slides, with no David Williams, and it was better”

Now, which of these two statements is true, I wonder.

Being here in Greece, I thought I would take my theme this evening and turn it into a discourse about fundamental Greek paradigms, and specifically about those two entities “mythos” and “logos”; myths and truths. Which of my statements about slides was a myth and which was the truth?

And even more specifically, I wish to explore the myths about biomaterials and translate them into truths of the real scenarios with biomaterials applications. Not surprisingly, I will focus on biocompatibility.

The terms “mythos” and “logos” describe the transition in ancient Greek thought from the stories of gods and heroes to the gradual development of rational philosophy and logic. The former is represented by the earliest Greek thinkers, including Homer, and the latter by Socrates, Plato, and Aristotle. In the “mythos” stage, the Greeks saw events of the world as being caused by a multitude of clashing gods – the gods for phenomena such as the sun, the sea and thunder, and gods for human activities such as winemaking, war, and love. As time

went on, Greek thinkers became critical of these myths and proposed alternative explanations based on observation and logical deduction. Under “logos,” the highly personalized worldview was transformed into one where phenomena were explained not by invisible superhuman persons, but by impersonal natural causes.

So let us compress the hundreds of years during which this mythos to logos transformation took place, to the fifty or so years we have had to examine the biocompatibility mythoi.

You may not like what I say and it is clearly your right to disavow my remarks and carry on as if you had not heard me. But I do ask that you listen. Remember Churchill’s:

“Men occasionally stumble over the truth, but most of them hastily pick themselves up and hurry on as if nothing had happened.”

And for full disclosure, let me say that I myself have to take some responsibility for the development and propagation of some of these myths. It was perversely some 10 years ago when I left Liverpool after 40 years of biomaterials science and moved to both North Carolina, at the Wake Forest Institute of Regenerative Medicine, and South Africa at our company Strait Access Technologies in Cape Town, to take up different phases of my life’s work that I realized that biomaterials and biocompatibility needed some re-assessment. You can find most of my thoughts in recent publications or you can ask me for a transcript of this speech afterwards and I will gladly send it to you.

This experience underlies a problem in science that is not often spoken about. Our conclusions are inherently biased by the nature of our experimental work and our hypotheses, where we instinctively look for evidence to support, at best, our honestly determined but incorrect ideas and, at worst, our strong and not-to-be undermined prejudices. It is good to get out of your own comfort zone, maybe your own laboratory, your own mind for a while; get out of your own bioreactor, get out of your scaffold, get out of your rats, and reconsider the totality of the evidence.

So now I come to the most important myths in biomaterials science, and the implications for their clinical translation .

Myth One: Mythos ena

We have a clear understanding of the mechanisms of biocompatibility.

The truth is that we are no way close to understanding these mechanisms.

I will provide an extremely important perspective on this point. It may not be entirely obvious in Europe, compared to the very litigious US environment, but there is an immense battle going on right now, at the heart of which is the so-called biological safety of biomaterials. It has so far largely remained in the realm of implantable devices but tissue engineering products will be

next. In full disclosure I mention here that I try to bring some sanity to this litigation through expert reports, but that is an uphill battle.

The problem is that medical device companies are pretty innovative – they have to be to survive. New devices are submitted to pre-clinical testing regimes, dossiers provided to regulatory agencies, and, all being well, devices are provided for patients, with a degree of caution that is dependent on the novelty and perceived level of risk. Patients sign informed consent documentation that explains all known risks.

Initial experiences are often good but then a few years later some problems are reported. Quite often success rates are higher than 95%, but the 5% that do not provide optimal satisfaction generate profound interest. Social media then takes over and very soon masses of patients claim a variety of symptoms, often non-specific but more and more these days based on putative, vague, autoimmune diseases. Usually the FDA forces a recall or the company voluntarily decides to withdraw from that market sector. The overall losers are the 95% of satisfied patients and the reputation of biomaterials science.

I am not saying at all that biomaterials could not be the cause of, say, autoimmunity, but causation has not been demonstrated and mechanisms are hard to find, but lay juries will make the decisions. The difficulty is that we do not know exactly how our materials interact with the immune system, and these interactions are clearly being seen to be of immense importance in biocompatibility. It is all very well me answering questions about the preclinical testing saying that the material passed cytotoxicity, hemolysis, pyrogenicity, in vitro mutagenicity and crude qualitative implantation studies, but we do not know about autoimmunity and obscure systemic effects because we do not know what to look for in pre-clinical models, or how, and, of course, were not required to do so at the time.

When it comes to explaining the biocompatibility of devices we have far too little knowledge of basic fundamental mechanisms. I have to say that I rarely see good scientific papers these days that focus on generic mechanism rather than on specific biomaterials developments. I doubt if the NIH is interested in funding this basic work, without which, of course, there will be no new successful applications. The emphasis is on translation, but without a really good scientific basis, there can be no translation – you cannot translate irrelevant science. More will be said of this later with other myths.

Myth Two; Mythos duo

Biocompatibility is a fundamental property of a biomaterial

Absolutely not. Zero marks for thinking it is, just as authors of papers submitted to *Biomaterials* when I was Editor-in-Chief who concluded that their biomaterial was biocompatible had those papers summarily rejected. The definition of biocompatibility, originally agreed at an ESB consensus conference in Chester in 1986 which I chaired, and

confirmed just last year at an IUSBSE conference in Chengdu, chaired by myself and Xingdong Zhang, is

“the ability of a material to perform with an appropriate host response in a specific application”

Biocompatibility clearly depends on the application, and on the situation in which a material is used. It cannot be a fundamental property of a material when it can vary so much.

Biocompatibility is not a property of a material but of a material-host system.

It is so disappointing to see the adjective ‘biocompatible’ which I thought I had banned decades ago, still being used by agencies such as the FDA, ISO and major journals.

Remember that there is no such thing as a biocompatible material.

Myth Three; Mythos tria

For all biomaterial applications, protein adsorption is the first event in biocompatibility phenomena, and protein behavior at the interface controls all subsequent events.

I have to admit that I, and many colleagues back in Liverpool 20 or so years ago, spent a great deal of time studying protein adsorption on biomaterials surfaces under in vitro conditions, and indeed, we studied cell behavior on such protein-adsorbed surfaces. I liked to think that we were adding to the sum of knowledge on biocompatibility but, with the possible exception of the work on the behavior of plasma proteins on silver surfaces, which did have implications with respect to the performance of some clinical heart valves, I cannot honestly say now that we contributed anything of true significance.

On leaving Liverpool and my laboratories behind, and examining so many papers submitted to *Biomaterials* that appeared to be repeating these mistakes, such that I more or less stopped accepting in vitro studies, I realized that a re-examination of the role of proteins at biomaterials surfaces was important. My analysis of published clinical biocompatibility data, over many years and in many different clinical disciplines, proved to my satisfaction that in most situations this hitherto critical event was of no consequence to ultimate performance. I published a perspectives paper in 2017 in the *ACS Biomaterials Science and Engineering* journal which made this declaration. There are some exceptions, of course, for example with protein coronas on nanoparticles, but I stand firm with my general conclusion.

Myth Four; Mythos tessera

For implantable devices, biocompatibility should be considered as a perturbation of wound healing, the so-called foreign body response being determined by overlapping but separate acute and chronic inflammation and fibrosis.

For several decades this sequence was considered to be the basis of the development of the fibrous encapsulation of materials, what we could refer to as solid-state biocompatibility. This was largely discussed without reference to any specific biological pathways, and more in the context of how monocytes, neutrophils, lymphocytes, macrophages, giant cells and fibroblasts could respond to the process of implantation. But such generalizations could not explain specific phenomena that were observed in clinical outcomes with devices, including excessive fibrosis around breast implants, intimal hyperplasia associated with intravascular stents and vascular grafts, late responses to polymer degradation and so on.

In the ACS paper I have just mentioned, I analyzed the evidence concerning the specifics of these and several other practical situations and concluded that we could consider the development of the host response in terms of series of pathways related to two distinct but potentially interactive types of phenomena, those of mechanotransduction and damage associated molecular patterns, so-called DAMPS. It is very important that we don't look for unique biomaterials-induced processes that you do not find elsewhere, which in retrospect was the difficulty with adsorbed-protein mediated events, but rather consider how the characteristics of biomaterials fit into processes that occur in physiological, and especially pathological, phenomena.

As you all know, mechanotransduction describes the molecular and cellular processes that are involved with the conversion of mechanical stimuli into biochemical signals. These have dominant roles in determining cell shape, proliferation, migration, apoptosis and other parameters, such that developmental biology, stem cell lineage specification, cancer biology, disease progression, and regenerative medicine are all powerfully controlled by mechanically stimulating events. When forces are applied, or more importantly when forces are changed, mechanotransduction pathways, involving sensing and signaling processes, lead to changes in gene and protein expression profiles. The time scale for these events may be milliseconds/seconds for the stretching of mechanosensors, hours for altered gene expression, and days or weeks for altered cell function and tissue development. It would seem intuitively obvious that because all biomaterials applications involve the perturbation of mechanical environments and, quite often, the deliberate application of forces that are unlikely to be of normal physiological character, mechanotransduction pathways should play a prominent role in biomaterial–host interactions. There are many biocompatibility phenomena related to implants, tissue engineering substrates, nanoparticle internalization and so on that I could primarily explain by mechanotransduction pathways.

As I have noted in this myth, the classical view of the host response to an implanted material involves acute inflammation, chronic inflammation, and fibrosis. However, these events should be considered as a continuum within the mechanisms of the immune response, especially in terms of the evolution of theories about inflammasomes, damage-associated molecular patterns, sterile inflammation, and the immunology of fibrosis. The biomaterials community has struggled with the implications of the involvement of the immune systems in biocompatibility since the former has traditionally been associated with the interactions

between hosts and pathogens, while the latter is associated with interactions between host and non-pathogens. The concept of the Danger Model, developed a number of years ago, replaces the standard self and non-self paradigms and is consistent with recently expressed views on sterile inflammation. In relation to biomaterials, and especially those medical products that have a long, residence time in the body, it is necessary to consider the progress of sterile inflammation from the moment of initial contact through to ultimate, clinical acceptance or elimination. The recent discussions about the immunology of sterile inflammation and fibrosis now allow such an analysis. It is important to note that the mechanisms of biomaterial-induced sterile inflammation have to be consistent with those that are implicated in similar conditions, especially sterile inflammatory diseases, including those associated with chronic inhalation of irritants such as asbestos, crystal deposition, for example of monosodium urate in joints leading to gout, and, possibly, atherosclerosis and endothelial cell dysfunction following engulfment of cholesterol, and Alzheimer's disease.

Again I have tried to explain most of these difficult-to-understand clinical biocompatibility phenomena using this sterile inflammation model, often coupled to mechanotransduction. I should emphasize that this is not an erudite yet academic exercise. If we understand these pathways, we could possibly determine methods to control biocompatibility. That is the reward here.

Myth Five; Mythos pente

For tissue engineering biomaterials, the most important specification is prior approval by the FDA for use in a medical device.

If you look at papers in the 1990s literature you will see many examples of this myth. It is easy to understand the rationale. Typical tissue engineering processes involved the formulation of a so-called scaffold and culturing cells within this, perhaps in a bioreactor with the addition of growth factors and maybe other agents, in the hope that new tissue would be generated. This involved new concepts which the FDA and other agencies were struggling with, so why not make it as simple as possible by using some synthetic biodegradable polymer for the scaffold that the FDA was already familiar with. Hence the widespread use of polylactic-glycolic acids, polycaprolactone and so on. The devices using these materials were typically sutures and simple drug delivery systems.

Let us see how this myth explodes. What does the manufacturer of such a medical device have to do to persuade the FDA of its biological safety? They have to show that the material has no effects on cells and tissues, using tests I will mention in a moment. In other words the material is harmless, with no intrinsic biological activity.

And what do we now believe tissue engineering is, and how should tissue engineering materials behave? According to my own definition, tissue engineering is the creation of new tissues for the therapeutic reconstruction of the human body, by the deliberate and controlled stimulation of selected target cells through a systematic combination of molecular and mechanical signals.

But how can we expect to create new tissue through a systematic combination of molecular and mechanical signals if our scaffold has been designed to have no intrinsic biological activity? How can we expect the tissue engineering biomaterial to replicate the niche of the target cells if they have characteristics of surface chemistry, energy and morphology that are diametrically opposed to the features of the microenvironment of the ECM that cells normally encounter.

The real life logos here turns the mythos on its head.

Lastly, myth Six; Mythos exi

We should continue to evaluate the biological safety of biomaterials by a panel of internationally agreed standard tests such as ISO 10993.

Manufacturers of medical devices have had to face this issue for a long time, and now it is starting to affect tissue engineering companies. Most regulators prefer manufacturers to follow widely recognized international standards for approval purposes. For biological safety this means ISO 10993, ISO being an industry-controlled standards setting organization. There are some twenty different parts of the 10993 series, with details for procedures to establish behavior with respect to cytotoxicity, sensitization, irritation, hemolysis, pyrogenicity, systemic toxicity, mutagenicity and so on.

And how does this work, exactly? For most tests, you take the test article, or a sample thereof, and expose it to a standard solution, usually for 72 hours and then test this solution, containing the components that have been leached from the sample in this period, and apply this solution to the test cells or animal sites.

In the context of the biocompatibility pathways I have just summarized, does this extraction – based test sound like a surrogate for the assessment of the biological performance of a new biomaterial?

A major factor is that with current test regimes it is almost certain that we cannot replicate the actual use in clinical practice, so how can we be sure of their predictive nature.

I have some suggestions.

First, with so many applications today, in order to avoid the many regulatory concerns and high cost associated with new biomaterials, most manufacturers keep to the same group of well-tried and tested materials. This is not a bad default position, except they are still usually required to conduct some of the 10993 procedures yet again. In the food industry there is a database of allowed substances, known as GRAS, Generally Regarded As Safe, which denotes additives that do not have to be repeatedly tested. Why should this not be done for biomaterials. Provided a biomaterial is sourced from a supplier with clear verifiable compliance

with detailed standard specifications, this could be the starting point for biological safety assessment.

If a material has no such track record and is not on such a list, then the risk assessment should start with full chemical characterization, as indeed suggested by ISO, but with a full, thorough evaluation of any toxicological concerns, performed by qualified experts who have detailed knowledge of both toxicology and biocompatibility.

I would then avoid the meaningless panel of in vitro and small animal qualitative or semi-quantitative tests and go straight to realistic large animal functional and biocompatibility studies, with regular functional imaging evaluations, regular veterinary and biochemical screening and full scale quantitative immunopathological analyses at autopsy.

I recognize that this would probably increase the costs and complexity of the risk assessment but I do think that the logic supersedes the testing myths we have at the moment.

Let me give you an example of difficulties with current regimes. As I mentioned earlier, we spend part of our time in South Africa, where, working with Peter Zilla, the Chris Barnard Professor of Cardiothoracic Surgery in Cape Town, we founded a company to develop innovative technologies to treat children who are dying from rheumatic heart disease, using techniques and devices that do not require open-heart surgery, which is essentially unavailable in much of Sub-Saharan Africa. Part of our technology platform is an intravascular, non-occlusive helical balloon catheter, which, incidentally, we were able to successfully use in a First in Man procedure this February. To obtain regulatory approval in other countries we are required to follow CE mark procedures, which means complying with ISO 10993. Part of our delivery device will be used in anticoagulated patients for 15 minutes, in association with valves that carry much higher risk. However, we were required to carry out in vivo thrombogenicity studies according to standard procedures, which were entirely unrelated to our application. We had to place the catheter in the jugular vein of non-anticoagulated pigs for 4 hours. Unsurprisingly our device, along with all control devices, clotted within the 4 hours and the test house we used determined that we failed the test, even though we had never seen a thrombus in all of our clinically-anticoagulated large animal development work. I have decided not to use a mythos – logos argument with the regulators and am waiting to see if they accept my milder rebuke.

Ladies and gentlemen, friends, I have discussed six biomaterials-related myths. There were, of course, many more Greek myths, and these often changed appearance and interdependence over time.

Just to provide some comfort to the doubters, let me say that the boundary between mythos and logos was not absolute at the time of Socrates, and never has been.

Even Homer, in the Odyssey, showed his reluctance to rely solely in his Gods:

Tell me, O muse, of that ingenious hero who travelled far and wide after he had sacked Troy; he suffered much by sea while trying to save his own life and bring his men safely home; but do what he might he could not save his men, for they perished through their own sheer folly in eating the cattle of the Sun-god Hyperion; Tell me, about all these things, O daughter of Jove, from whatsoever source you may know them.

Logos was increasingly seen as the domain of truth, but mythos was still present in the everyday lives of the people. The two ways of thinking are both important to this day, especially for religious people: they complement each other. Where logos is concerned with practical matters, mythos offers meaning. Myths and other religious texts are not usually reasonable and do not empirically prove anything, but for many people they can offer a way to make sense of things that logos cannot explain.

As Grecian society went through a transformation, they forged relations with other nations, which meant that the merchants came in contact with more different cultures than ever before. On top of that, there was a rise of new scientific ways of thinking, including the development of philosophy and rhetoric. Philosophers realized that words have the power to manipulate factual reality, and thus, that 'truth' is subjective – much like today. Because they discovered more and more about the unknown, people increasingly relied on a more rational mode of thinking, but developed mythological stories into art-forms, including poetry.

So, what I have told you tonight, given in all good faith as logos, may still not be the total truth and it is up to you to challenge these concepts, but I hope that you will not do so by quietly going back to the original mythos.

In my defense I should explain that the Welsh are well known for combining mythos and logos. This dates back to the time of Taliesin, Chief of the Bards, living some 1500 years before Dylan, for whom records show him to be a "mytho-historical character", ally of King Arthur, but a powerful poet in mid and north Wales, who mixed real events and people with entirely mythological ones. He mixed disdain for lesser bards with ennoblement of his own position :

**"Be silent, then, ye unlucky rhyming bards,
For you cannot judge between truth and falsehood.
If you be primary bards formed by heaven,
Tell your king what his fate will be.
It is I who am a diviner and a leading bard,
And know every passage in the country of your king;**

And that is why, present company excepted, and apart from the spheres of rugby, music and poetry, the Welsh have struggled to make their mark in the modern world.

And as a final point, when I was working in Liverpool, Peggy and I lived on the edge of a forest in rural Cheshire, overlooking the English-Welsh border, where in one direction we faced Lake Bala where much of Taliesin's activities occurred, and in the other direction, over the Mersey,

we faced Liverpool, and the famous Anfield. In thanking Dimitrios and UEFA for arranging that my speech did not clash with the Champions League Final, in Madrid in two days time, I will present you with my last examples of Mythos and Logos

Mythos says Tottenham will win

Logos says that Liverpool will be Champions tomorrow.

Ladies and gentlemen, please do go gentle into your good night,

Good night

Footnote: Liverpool did indeed win two days later, to become European Champions.