

INSTITUTION OF MECHANICAL ENGINEERS

THE SMITH & NEPHEW LECTURE, 2006

modified version of the lecture
presented to Sir Christopher O'Donnell
and members and guests of the Medical Engineering Division

*To Engineer is to Create
The Tissue Engineering Vision*

Presented by

Professor David Williams
Director, UK Centre for Tissue Engineering
at the
University of Liverpool

Sir Christopher, Ladies and Gentlemen

I am very pleased and honoured to be here this evening to present this Smith & Nephew lecture to the Institution of Mechanical Engineers. I have had an intermittent but very valuable professional relationship with Smith & Nephew going back many decades, having visited the Gilston Park laboratories many times in the 1970's and 1980's, and having had a number of students and post docs graduate to become employees of the company over the years. Moreover, although I am not a mechanical engineer, I am nonetheless an engineer, of the materialistic variety and, as Fellow of our umbrella Royal Academy, I feel quite at home here.

I have chosen this title: To Engineer is to Create - The Tissue Engineering Vision. I shall be discussing new concepts that address the question of what engineering really is, and painting some exciting images that hopefully will be translated into therapies that could revolutionise the treatment of disease and injury.

Let us get straight to the point. Teleologically, the human body is supreme, at least when in its prime condition. But as we all know, time moves inexorably on and we, as individuals, cannot keep up. We age.

As a metallurgist I can say quite clearly that my profession is the personification of old age. As we get older, we see silver in the hair, gold in the teeth, lead in the feet and iron in the soul.

On growing up, I changed from a metallurgist to a medical engineer, indeed an implantable device medical engineer, where we now see titanium in the teeth, platinum in the nerves, silicones in the breasts, hydrogels in the eyes and polyurethanes in the arteries. Not so lyrical, perhaps not so elegant, but these have made a major difference to our way of life, and, as we shall see, to our way of death.

And now I am a tissue engineer, not, as Christopher Reeve once remarked a designer of Kleenex, but a proponent of regeneration, where we have scaffolds to support the reconstruction of our bodies, growth factors recapturing our youthfulness, genes turning us on again, and stem cells transforming us from discarded waste to multifunctional tissues and structures.

What a journey, in 40 years from a PhD in body centred cubic metals to a Fellowship in body enhancing organs.

And so we age; we deteriorate, we senesce, we ache, we forget, we remain unhealed, maybe ulcerate. Things that used to work no longer do, for which some people are, of course, ever grateful. We do not see so well and have to use glasses, maybe not hear

so well, perhaps have salivary gland dysfunction and need to imbibe water now and again when we speak.

Smith and Nephew is, of course, here among these conditions, attempting to redress some of these imbalances, especially with the degeneration of the musculoskeletal system and the loss of tissue and structure in the degenerated hip joint. I will say no more about this particular Smith & Nephew favourite place until the end of this lecture, but please keep this image in mind.

But I will say this. Smith & Nephew is one of those companies that have straddled the interface between medical device technology and tissue engineering. As with anyone who straddles a fence that is just that bit too high, it can be uncomfortable, each wobble, perhaps by a regulator, an investor or a joint venture partner, prodding the most sensitive parts, including the bottom line perhaps, and you move this way and then that way, trying to achieve the most comfortable position. And, as the cognoscenti will appreciate, the mere mention of Dermagraft will ignite those feelings and stimulate the players to argue firmly for one side or the other, but not the middle ground.

So what is tissue engineering. How does it differ from medical technology and which way is it going right now. How can we translate these colourful images into beneficial therapies. If I, for the moment the metaphorical epitome of ageing, develop incompetence in a heart valve, here incompetence being a technical term to describe a condition of inadequate control of blood flow rather than a derogatory term that describes incapacity of neurons, I can have it replaced.

A wonderful example of a synthetic man-made, conventionally engineered metal, carbon and textile composite, that looks absolutely nothing like a natural heart valve, but which has a 95% chance of being still there and fit for purpose 20 or more years later. The recipients of such valves will more than likely die from totally un-related causes rather than any malfunction of the valve, where the biggest risk factors involve the inability to remember the daily dose of anti-coagulant and the high risk of divorce from the partner who can't stand the sound of the valve clicking away during the dead

of night, which of course should be infinitely better than the lack of clicking, which announces the dead of the night.

What an interesting dilemma we have here. A medical device, not outrageously expensive, which can, and does, save many lives, but with some disadvantages. The drawbacks almost entirely relate to the fact that the valve is synthetic. I can't emphasise this too much; a synthetic material does not grow but it does fatigue and creep. Slow crack growth rather than slow valve growth in a child is a fatal combination. The materials may be as chemically inert as we can make them, but physiologically inert they will not be, hence the reason for daily anticoagulation, since any foreign body within the central circulatory system will, sooner or later, cause a fatal blood clot unless we proactively pre-empt that event with regular cumidin or warfarin. In my experience, in this situation, mostly within litigation, I have rarely come across a case of a fatal clot in a heart valve patient without the compliance of that patient with the anticoagulation regime being a major risk factor.

I remember meeting Christiaan Barnard a number of years ago and he told me that in the early days of valve replacement he operated on a young girl from rural South Africa. On the follow up visit a couple of months later he asked the parents if they were giving the child the anti-coagulant and they said no, they weren't. He strongly remonstrated with them, following which they went back home and gave the child the whole bottle and she haemorrhaged to death that night.

To get back to the main story, the truth is that we have some exceedingly good biomaterials that are used in some very successful devices, including titanium and platinum, PTFE and polyethylene, carbon and alumina, which, unless they are able to initiate one of the few autocatalytic biochemical cascade processes, by which I mean the blood clotting cascade and the complement activation cascade, both of which could be fatal, and unless they are subjected to a significant erosion or degradation process such as wear or fretting corrosion, all of which can be prevented by appropriate design, they should outlive the patient.

A number of years ago, and amidst a mass of publicity some of you may remember, one type of heart valve, the Bjork Shiley valve, probably the best haemodynamically

designed valve of its generation, suffered some fatigue failures. These occurred, coincidentally as it happens, at the site of welded joints that held one of the struts to the annulus. Several hundred people died, which of course was a tragedy, even though this was less than 1% of the population that received the valve and had their lives saved. Of course litigation and compensation followed in the US. This was the first valve that fractured in the UK, actually in a patient in Liverpool, and I was asked to give evidence at the inquest. At that time there was little of a compensation culture in the UK, and lawyers were not able to operate on the basis of no win no fee, so there was not much fuss and the coroner agreed with me that, tragic as it was, it did amount to accidental death. My evidence was discussed briefly on Radio Merseyside that night, which was unremarkable except that the young reporter, whom I noted had slept through much of the inquest, got a little mixed up and announced that a nuclear powered pacemaker had exploded in the patient. A telephone call to the late night news desk persuaded them to correct this part of the story so that Merseysiders could sleep a little easier in their beds. However, there was one consequence, in that a solicitor heard the story and persuaded one of his clients to take some action, because her husband had had a replacement valve some years before and had died suddenly 18 months previously. The solicitor thought that she could find out whether he had one of these defective valves and seek compensation if he had actually died from a valve failure. Bizarrely, a few days later in my office I received a visit from the Police, which did my reputation and street cred in Liverpool quite a lot of good, and with a pathologist colleague was instructed to attend the exhumation and examine the said deceased and his valve. I had the pleasure of submitting a report to the coroner which said that amidst the rather disgusting mass of decay, the only thing that shone brightly and was still in good working order was the replacement heart valve.

So far, so good. We can replace and correct some parts of our body when they go wrong, and we can get decades of good performance out of many of these devices, including the life saving intravascular stent. But what is it exactly that these implantable devices can do. The heart valve that I have discussed a few times here is basically a simple mechanical structure that can crudely control the flow of blood through the heart, and that is all. A hip replacement transmits forces from pelvis to femur and allows movement of that joint, but it doesn't take part in the metabolic and physiological functions of bone. The intraocular lens in the eye allows for light

transmission through to the retina in patients with cataracts, the dental implant allows mechanical functions such as chewing and permits some aesthetic reconstruction of the dentition. The breast implant fills a space, the pacemaker supplies electrical signals to the heart to permit proper rhythm control and the implantable defibrillator will shock the heart if that rhythm becomes unstable.

Don't get me wrong, these are all important functions, but they are the physical or mechanical functions of synthetic replacements and not the biological functions of the normal host tissue. Conventional engineering, be it mechanical, or electrical, or metallurgical is not good enough to replicate both structurally and functionally all diseased or damaged tissues and we have, ladies and gentlemen, some serious deficiencies. Do we have a device to treat macular degeneration, an increasingly common cause of blindness in the aged? No, and we are not likely to. Do we have a device to treat Parkinson's, a neurodegenerative disease affecting more and more people? Yes, we have a deep brain stimulator that can treat the symptoms in a very small percentage of patients, but otherwise no. And there is nothing for Alzheimer's. At the moment we have no device based therapy for diabetes, the synthetic replacement of that troublesome intervertebral disc does not yet exist, although we can, of course mechanically fuse the surrounding vertebrae. We have no synthetic bladder, uterus, penis, prostate gland or stomach.

So let us engineers think a little differently. To engineer does not necessarily imply the manufacture, to standard specifications, in a factory, of multiple numbers, a product that can be classified, compartmentalised, placed in an inventory and marketed.

The engineer is by definition a creator. The engineer creates ideas, generates solutions and reduces them to practice. As the title to my presentation says, to engineer is to create. The original creator, we are told, created man in his own image. In spite of what we hear in the press, we cannot create new individuals de novo, even taking into account the advances in cloning, and we should have no desire to do so. But we can, now, create new tissues in compromised patients. Tissue engineering is the creation of new tissues. It is a component of the relatively new area of regenerative medicine.

I define regenerative medicine as any therapy that aims to induce the regeneration of tissues or organs following disease or injury, or in the presence of birth or developmental deformities. This may be achieved by gene therapy, cell therapy or tissue engineering, or indeed in a combination of these. The issue is this. We as adults have largely lost the ability to regenerate tissues. We had this ability as a foetus or embryo, by definition, as we did as growing children, but then we lost it, or in fact gave it up in the spirit of evolutionary changes. A few tissues or organs can be regenerated, and usually for good practical reasons as with skin and bone for example. Without limited skin regeneration we may never recover from common skin wounds and readily die of infection, and without bone regeneration, we would never recover from bone fractures and remain forever immobile. We also know that a number of organs have a modicum of regenerative capacity. But, by and large, evolution has determined that most tissues lose this capacity so that we have little armoury to defend ourselves against the degenerative diseases and trauma. Under some conditions we are able to repair ourselves, but usually with poorly functional fibrotic or scar tissue, which is not usually the same, either structurally or functionally as the damaged tissue, as a heavily scarred burns patient will unaesthetically demonstrate, however we try to treat them and as a spinal cord injury will physically reveal through paraplegia. Repair is not regeneration, at least in most circumstances. And let us get back to a more aesthetic slide for the moment.

What we would really like to do is switch back on, under the appropriate circumstances, the ability to regenerate ourselves. I am going to leave aside gene therapy for the moment since that is a little different to the other procedures, but move quickly through cell therapy to tissue engineering. Cell therapy involves any technology that relies on replacing diseased or dysfunctional cells with healthy functional cells. There is nothing else involved apart from a delivery mechanism, which is usually a simple injection system. The cells do all of the work.

We have to choose the right cells, optimise their condition so that they can function properly in the desired manner, which may mean switching on some functions, or differentiating stem cells down the required pathway, typically through the transient action of growth factors, and deliver them to the required site. By and large cells, of which you see a few here, come in all shapes and sizes and functions, and do what

they want to do, and what they do best under their normal conditions, and it is not a trivial matter persuading them to do otherwise. But it is possible and then we have the prospects of a functionally regenerated tissue, which could be the dopamine producing tissue to resolve Parkinson's Disease, or cardiomyocytes to treat the heart after an infarction.

Cell therapy works for some systemic conditions relating to blood disorders and to some highly localised conditions where the delivery of cells and their maintenance, can be precisely controlled and where it is cellular function and not tissue structure that is required.

This is where tissue engineering comes in, and here is the vision.

Not where the engineering tools are fashioning the shape of the wood tissue, but aiming for the regeneration of tissues that are functionally and structurally analogous to the diseased or traumatised tissue they are intended to treat. If we have damaged cartilage, we wish to regenerate new cartilage, and bearing in mind that cartilage differs in structure from one situation to another, we want the right new cartilage for that specific traumatised cartilage. If we have damaged nerves, from spinal cord to peripheral nerves, we want to regenerate those nerves and re-establish connectivity, primarily to return sensitivity and mobility. If we have dysfunctional urinary, genital, digestive and respiratory systems, we would like to be able to regenerate bladders, prostates, intestines, lungs or whatever is the primary cause of the dysfunction.

Tissue engineering is, by my definition, the persuasion of the body to heal itself, through the delivery to the appropriate sites of molecular signals, cells and / or supporting structures. Engineers may start to see where they come into this picture on reading this conceptual definition, since we have cells, which sounds like the role of the cell biologist, and molecular signals which sounds like the combined role of pharmacologist and molecular biologist, but also supporting structures which sound like the role of the materials scientist and chemical or mechanical engineer. But it is more than that, as a more recent definition suggests; the creation of new tissue 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. The controlled stimulation, the systematic combination of molecular and mechanical signals – the epitome of a classic systems engineering approach to a complex problem of creation.

Consider how this might be done, using my central tissue engineering paradigm. We start with cells. These could be autologous, being derived from the patient themselves. I should digress for a moment here to say that these could be fully differentiated cells, such as chondrocytes to regenerate cartilage, combinations of keratinocytes and fibroblasts to regenerate skin, osteoblasts to regenerate bone, combinations of endothelial cells and smooth muscle cells to produce blood vessels and so on.

Alternatively they could be stem cells, that is those cells which are capable of differentiating into committed cells. Mesenchymal stem cells derived from the patient's bone marrow is one obvious source, but peripheral blood and adipose tissue are also good sources, the latter being of immense importance, being the basis of my earlier statement of stem cells transforming us from discarded waste to multifunctional tissues and structures, since the obvious source of adipose tissue is the ever more freely available product of liposuction. Think about it!

Autologous tissue engineering has many advantages, especially as the regenerated tissue is, literally, the patient's own, so there should be no questions of an immune response, but there are huge problems of health economics here as a whole, sterile, production line has to be set up for each individual patient, and business models are hard to define.

The alternative is the allogeneic cell source, being donor derived. These can be expanded lines of individual cell types, which can be sourced and maintained on a commercial basis in order to treat a multitude of patients, or embryonic stem cells, derived from unwanted, or surplus – to – requirement embryos. This, of course, has enormous ethical dimensions, which I am not going to discuss because of time limitations, except to say that at this stage I really believe from technical and safety perspectives, the adult stem cell route is in the lead.

Having derived the cells they have to be optimised, that is expanded, or differentiated, or in general, manipulated in some way, in order for them to be presented in the right concentration and condition, they then have to be persuaded to express the right type of tissue, which usually requires some supporting structure, often referred to as a scaffold, onto or into which the cells are seeded, and which will usually biodegrade as the tissue forms. This takes place in a bioreactor with an appropriate combination of fluid shear stresses and substrate mechanical stresses to deliver the mechanical signalling, and with the delivery of reagents to provide nutrition and the signalling to persuade those cells to express the extracellular matrix, which is usually the essence of the structural tissue, for example collagen, elastin or a glycosaminoglycans. This signalling is most often achieved by means of growth factors, cytokines or chemokines.

It may also be necessary at this stage to alter some of the genetic characteristics of the cells, preferably using some non-viral vectors, in order to improve their efficiency, bearing in mind that these cells do not normally produce this regeneration in the adult world and are being persuaded to do so by us engineers. Transfection of chondrocytes with the transcription factor SOX 9 assists in maintaining their phenotype and improving efficiency.

With luck, we then have a piece of tissue, preferably perfectly matched to the patients requirements and the clinician then has to place it in the patient, where it has to be fully, functionally incorporated into the host. This is not a trivial process since we have to control those events which we do not want to happen and induce those which are essential for this incorporation and function. Again, bear in mind that we are switching back on a process which does not normally take place at our age, but then we need to switch it off. In particular we have to ensure that we do not have the uncontrolled proliferation of tissues, otherwise known as tumour development, which is a major safety concern with embryonic stem cells, which are known to be capable of teratoma formation. We also have to control the inflammation associated with the presence of a degrading biomaterial scaffold, perhaps with the sustained delivery of non-steroidal anti-inflammatory agents, or to control the immune response to allogeneic cells through some form of immunomodulation. We have to ensure that there is no toxicity or hypersensitivity to process additives and of course no

microbiological contamination. On the other hand we do want innervation and, especially, angiogenesis or vasculogenesis, which is the formation of the appropriate blood vessel structure.

In this way, just invoking this central tissue engineering paradigm, we do have the prospect of generating and incorporating new tissue into patients for the treatment of disease and injury. It is not necessary, of course, to follow this precise paradigm and there are many potential variations. We have a multitude of scaffold and matrix possibilities.

We have many variations on the bioreactor concept, up to and including the use of the patient's body as the bioreactor. There are combined cell therapy and tissue engineering approaches, especially to those situations involving organs, where cells may be immunologically protected by polymeric micro-encapsulation, as with the encapsulation of Islets for the tissue engineered pancreas in the treatment of diabetes.

So you see that these are very complex processes, which therefore constitute a complex challenge, and a complex vision. Is it feasible, and where are we with the delivery of that vision? I suggest to you, Ladies and Gentlemen, that the vision is indeed valid and that tissue engineering will play an immensely important role in the treatment of disease, not competing with the pharmacological and medical device sectors but acting in a complementary fashion to deal with those conditions for which there are currently no effective therapies.

It is true to say that we have not been startlingly successful so far, either clinically or commercially, but it is early days.

From a commercial point of view, business models have been difficult to identify, and the slowness and inconsistencies of regulatory and reimbursement schemes globally have much to answer for. But I do believe that the corner has been turned. Whether Smith & Nephew agree with me is an interesting question, having been at the forefront of developments for a long while but having had some finger tissues burnt by these difficulties.

From a scientific point of view, we also have a long way to go, and it is vital that we control the hype and the expectations until we really have something to shout about.

From an engineering point of view, we have to recognise, and promote this recognition, that here we have a massive opportunity, which is not confined to the manufacture of scaffolds, albeit it through sophisticated rapid prototype of other state-of-the-art processes, nor to the design of bioreactors to match any of those in biotechnology and biomanufacturing, but which encompasses the whole process, the whole paradigm, a true systems engineering challenge.

From a clinical point of view, the patient is the most important stakeholder. Where does he stand? Well, perhaps he stands right here.

I showed this slide at the beginning, of painful arthritis and asked you to retain that image in your memory. The reason I did that was as follows. I have not mentioned osteoarthritis as a target for tissue engineering. Generally we have very good techniques for the treatment of osteoarthritis, with conventional medical device technology.

Total hip replacement now gives in excess of 90% success for 15 years. Although not without some problems, which I do not have time to discuss here this evening, this is a very successful and routine procedure and I do not see a role for tissue engineering in the routine treatment of osteoarthritis; there is no unmet clinical need here. I believe that I am in a good position to say this, having been involved with the development of materials for total joint replacements from the late 1960s onwards, but also because the picture you are looking at is my own hip, which was duly reconstructed a few months ago, based on the degeneration that previous radiograph showed. It is a successful, low risk, economically efficient procedure, in my case involving highly efficient and robust titanium and alumina.

I have one caveat to this statement, One problem with osteoarthritis is that we do not recognise, give or take a twinge or two, or a moment of discomfort whilst exercising, that we have such destruction going on for many years, bearing in mind that all of us have some degeneration of our cartilage to some extent from about the age of 18

onwards, and by the time it is clinically diagnosed, the destruction of both cartilage and bone is so far advanced that a tissue engineering solution is probably beyond reach. If there were better screening methods for arthritic changes to be detected earlier and cost effectively, then tissue engineering may have a role in the slowing down of these changes much earlier in life.

I will extend these comments to say that those situations where we have very good and effective treatment modalities at the present time are not the targets of tissue engineering. Here I include heart valve disease in the elderly, although not necessarily in paediatric cases. I include most forms of restorative dentistry, which are highly effective, the treatment of cataracts, and so on.

Unmet clinical need should be the target. Diabetes, both the disease itself through the tissue engineered pancreas and its consequences, through the treatment of chronic ulcers, is high on the list. So are several diseases of the cardiovascular system, including heart failure, diseases of the retina, primarily macular degeneration, neurodegenerative diseases, obviously Alzheimer's and Parkinson's, regeneration of the bladder in children and of bladder control sphincters in the elderly and perhaps the aesthetic reconstruction of the face.

These, Ladies and Gentlemen, are the tissue engineering visions. I attended last night the Royal Academy of Engineering and Lloyds register annual lecture on Risk, given by Sir Robert Worcester, founder of MORI polls, at the Royal Society, about the public perception of risk. One statistic he showed was of immense importance to all of us here, and a frightening statistic it was. In a poll to determine public perceptions of scientists and engineers, zero per cent perceived that engineering has any connection with medicine. Zero percent. As I am sure you will agree, engineering is, literally at the heart of much medicine, and I would like to think that tissue engineering now forms a major platform within medical engineering.

The engineering of tissues, using materials to control cells, is neither dream nor sinecure, no nightmarish manifestation of those who attempt to play God, but a very realistic, even if still challenging, paradigm for addressing those conditions of disease and trauma that other therapies have so far failed to resolve. For those who grow old

in discomfort, in pain, in dysfunction, just consider what creative engineering may be able to do for you.