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The biomaterial horizon

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In this beautiful location of Davos, it is easy to ascend a mountain from which you can look all around and witness an incredible panorama. If you are new to the area, the view is one of a rugged horizon which would appear to be similar in appearance in all directions, especially in winter. That is not unusual; there are many places in this world where the horizon, whether beautiful or unappealing, appears to be the same in diametrically opposed directions.

The horizon is the place where earth and sky apparently meet. Earth is the reality, typified by our expression, "Down to earth". The sky is the unknown, the blue skies of optimism, the grey skies of pessimism. The earth and the sky meet at some distant inaccessible place, which provides us with the security of knowing where we have come from and the excitement of the unknown future.

I stand here today, having been in the field of biomaterials for 25 years. That is a long time. And I stand here looking both backwards and forwards to scan the biomaterial horizon. And I have to say that I am often not sure in which direction I am looking. Nor is the forward horizon necessarily one of blue skies but rather one of greyness, potentially of cumulonimbus character.

Twenty-five years ago, we had few journals in the field, but the subject matter in them reflected the use of silicones, PVC, titanium, cobalt alloys, polyethylene and a few other materials. I look at the present and I see the same materials, and a few others being discussed in today's journals. If I look back to the principle concerns 25 years ago, polymers wore and their debris produced a tissue reaction, metals corroded and metallosis became a problem, plastics in contact with blood produced thrombi and solid-state carcinogenicity was already controversial. A glance at today's menu and it is *deja vue*.

Of course progress has been made; it would be a serious but wildly inaccurate inditememt of all of us here if that were not the case. We have today a much greater understanding of the issues of biocompatibility. We have a much more powerful and sophisticated array of devices to be used in the treatment of a wider and wider group of patients. We have some far better structural materials, ranging from high performance composites, thermoplastic elastomers, superalloys and tough or bioactive ceramics. And we have new surfaces, such as produced pharmacologically, biomimetically, by cellular or protein engineering or by physico-chemical means. But it is with their appropriate exploitation that I am concerned such that we can ensure that the biomaterials on the horizon, near or far, can enhance the health of the nations and their peoples.

So, with one eye on the past and the lessons which should have been learnt from the receding horizon, let me look to that future horizon, first pointing out the grey clouds and then speculating on where and when the blue skies will appear, and, hopefully not arrogantly, but based upon a few years of experience, suggest how we might benefit from those blue skies.

The concerns that I express are largely based upon the difficulties facing the medical device industry, without which, of course, there can be no successful exploitation of biomaterials. I regret that these concerns are largely non-scientific, but that is the nature of the world we live in today.

Thirty years ago, the media started to become interested in biomaterials because medical devices, especially in critical situations, were starting to bring relief to patients and to save lives. Renal dialysis was starting to make a marked impact in patients with end-stage renal disease, and soon prosthetic heart valves, aortic vascular replacements and cardiac pacemakers were items of important news because of their obvious benefits.

Twenty years ago, total hip replacements were the focus of attention and soon new composite materials for tooth reconstruction and hydrogels for use on or in the eye were gaining the public's attention. The media loved these stories because of their human interest value.

But then the climate of opinion started to change and the interest became rather negative, since we all know that the media loves the bad news rather than the good. Controversial issues such as the total heart replacement story did not help but it was the Dalkon Shield intra-uterine contraceptive device, the ascending infection of which caused severe morbidity, the Bjork Shiley high angle heart valve malfunction which contributed to several hundred deaths, and more recently the breast implant phenomenon, the problems with temporomandibular joint replacements and the public controversies over the safety of silver–mercury amalgams and certain dental alloys, all of which I will discuss a little later, that have turned the media, and with it public opinion, away from rather than towards the benefits of implantable medical devices.

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The origin of the problems lies, naturally, with clinical failures. That they occur is not in doubt. I would like to deal with their causes and consequences in relation to the following issues:

The expectations of patients
Litigation
Media responsibility
Manufacturing, engineering and scientific responsibility
Clinical trials and regulatory approval
Surgical expertise and skill

First, the expectations of patients. There are real, albeit small, failure rates for pharmaceuticals and for surgical procedures in general and patients are usually well informed. If, however, we attempt to replace defective or diseased tissue with prostheses, can we expect to use man-made synthetic structures and have perfect success? Of course not. So let us be honest with the patients and provide information about how successful the devices are expected to be. To hear the testimony of patients who have been devastated by the failure of a device saying that they were never told there was even a remote possibility of failure, and indeed to hear, as I did a few months ago, a manufacturer stating in a public forum that his device could never fail in a patient, underlies what I believe is a significant problem.

For if, as a patient, you undergo a procedure which could be one of the most significant occasions of your life, and you are led to believe that the device itself cannot fail, but it does, you are far more likely, or worse still your surviving relatives are far more likely, to feel very aggrieved and to think of consulting lawyers to seek legal redress and compensation. And it is legal action, or the threat of legal action, which has been driving the medical device business in recent years.

Clearly, everyone has the right to seek compensation if they are injured through neglect, and any manufacturer who is found guilty of neglect must be dealt with, bearing in mind that manufacturers are liable for negligence in design and manufacture, disregard of community standard practices and failure to inform of hazards and precautions associated with the use of their products. There are clearly differences between the rare cases of negligence through commission and the more frequent cases of oversight, and appropriate balances should be maintained, but the experience in the United States, slowly but surely moving in this direction, takes this point to absurdity, which leads me to my second point.

I recall so well and so vividly, my experience working with a pathologist at a post mortem on a patient who had died 18 months previously of what was recorded at the time as heart failure. The body had been buried, but later a lawyer, hearing about heart valve failures, advised the family of the deceased, who himself had had a Bjork–Shiley high angle valve fitted some six years before his death, to have the body exhumed and the valve inspected. If valve failure had occurred, then they could sue the manufacturer. It was not a pleasant experience but we were able to report that not surprisingly, the only thing still recognizable and in good working order was the artificial valve. The wife, who had only just come to terms with the death, then went through even more emotional upheaval.

The failures of one type of heart valve and the associated legal and fiscal implications, have naturally had a profound effect on the heart valve industry and, indeed beyond in the broader medical device sector. Equally, the current problems over breast implants has caused major and minor manufacturers to withdraw totally from this business. Moreover, litigation currently in progress in connection with the supply of a raw material to a device manufacturer who utilized the material to form a composite which was part of a device that failed in a large number of patients, wherein that raw materials supplier, DuPont, is being charged with the responsibility of the clinical failures, simply because it is one of the worlds largest companies and was assumed to have unlimited financial resources to pay the damages, has caused that company to reassess its policy of supplying materials to the medical device industry, the net result of which is likely to be the withdrawal of many products from the marketplace. Some five or so years ago I had published an article in a UK national newspaper in which I predicted that unless caution was exercised in this matter of litigation, instead of there being large numbers of successful treatments marred only by a few failures, there would be no successes because there would be no devices to implant. A successful action against a company resulted in the award of millions of dollars including punitive damages so the company would learn its lesson. I think we can all appreciate exactly what lesson it will choose to learn.

As biomaterials scientists and clinicians, we appear to be impotent in all of this, but I would say that we do have some duties. Litigation often thrives on assumptions and, in medical device cases, the causes of failure, and indeed the causal relationship between clinical symptoms and material characteristics or device design are very difficult to establish or conversely, to deny. The battle already started in the breast implant story, and about to escalate in the courts, is a good example. The cause is said to be the silicone, the effect is said to be auto-immune disease, the mechanism by which such a polymer can induce conditions such as scleroderma or rheumatoid arthritis being totally unclear. The judgements will depend on the testimony of so-called experts, where it is so easy to become embroiled in the emotional arguments on one side or the other. We, in the biomaterials community have a potentially crucial role and I urge the most sincere professional restraint, caution and unbiased wisdom in such cases. It is too easy to see advice, comment and indeed judgements being given by people unencumbered by a knowledge of the facts.

In this context, let me return to the subject of the media. In dentistry I recall a number of years ago the question of mercury toxicity becoming a matter of public concern, especially again in the United States. I am still not at all convinced that there is any causal relationship between dental amalgams and a variety of

neurological and neuromuscular disorders, such as multiple sclerosis. However, a few influential people, some sincere but some acting out of self-interest, made these exaggerated claims, in a media campaign, and the public, not surprisingly became very concerned. There is a clear need to distinguish between symptoms directly linked to the usage, for example the effects of dental materials on the oral mucosa, and these inferential symptoms, and it has to be recognized that this is extremely difficult. However, many people spent large sums of money having all their amalgam fillings removed and replaced by composites on the basis of this. Now, I am an advocate of composite technology in dentistry and would be happy if amalgams were never used again, but it is reprehensible to conduct a vendetta in public in this way and give sufferers of such diseases false hope. German colleagues are no doubt aware of the current, highly public debate, largely conducted on the television and legislative chambers, about the putative role of palladium in causing systemic manifestations following the use of palladium–copper alloys in prosthodontics.

Again we may appear to be innocent bystanders, unable to enter the debate. On two occasions recently, with respect to heart valves and breast implants, I have been questioned and interviewed for programmes on British television, only to have my comments edited out because I have not been able to follow their line that the 'evil' manufacturers have to be exposed on the air. A cautious, scientific statement, without emotion or bias, apparently does not appeal to the audience. The media, and indeed the general public have difficulty in interpreting scientific objectivity, generally believing that a view which takes both sides of an argument into account must be based either on indecisiveness or ignorance. Let us not be disheartened by this type of experience, however, and take whatever opportunities we have to interject rationality into debates that become of public concern. I would just as much hate to see the biomaterials horizon drawn by the media as by lawyers.

Now let me turn to the subject of manufacturing and scientific responsibility. In the real world it is inevitable that marketing is a powerful force; that is a fact of life. But markets can only be successfully exploited if they are based upon appropriate and cost-effective technology. And when we come to consider the real causes of failure of medical devices, we know that we don't always get the technology right. In discussing technology I draw attention to the phases of product design, materials selection and treatment, quality assurance and product testing.

Would anyone deny that some of the problems that we currently see with excessive wear of some knee joint prostheses are related to inappropriate design, that some failures of heart valves were caused by inadequate quality assurance or that many failures, either overt, frank failures, or simply failure to meet expectation can be attributed to an inability to effectively predict clinical performance prior to use. I will return to the latter point in a moment, but the real point of this statement is that we do have a good selection of biomaterials, we do have appropriate procedures for product design and quality assurance. Let us use them effectively and let us be realistic and learn the lessons from the past.

My first involvement in biomaterials was as a metallurgist, working with an orthopaedic pathologist on corrosion and the tissue reaction to corrosion. I have to be honest and say that I had thought by the mid 1970s all the problems had been solved and all the lessons learnt. We saw corrosion of stainless steel induced by intergranular carbides, by lack of molybdenum, by designs that involved too many crevices and too much fretting. We saw galvanic corrosion whenever dissimilar metals were coupled, including two chemically or microstructurally different variations of the same alloy. We saw tissue discolouration around titanium, and explained it, and discussed the unusual but perfectly acceptable histology. We saw corrosion fatigue in some alloys and discussed endurance limits and so on. Now we find modular orthopaedic systems, coupling two different alloys at the interface at which is micromovement. And we are getting fretting, galvanic and crevice corrosion again. Titanium is used in inappropriate circumstances and we see extensive discolouration and greater tissue reactions than this excellent metal deserves. This is what I mean by *deja vue.*

However, let me utter a few words of warning. Let us not assume that the application of state-of-the-art technology from other engineering fields will right the wrongs in medical devices. Diamond-like carbon coatings for bearing surfaces are an attractive concept but no coating will correct for poor choice of substrate material or poor mechanical design. Heparin grafting on surfaces is also a good idea but will not work in the presence of poor haemodynamics.

Which leads me to cost effectiveness. Many will know that the subject of intra-ocular lenses is of current interest, largely because of the perceived need to reduce inflammation around the lens and thereby reduce complication rates. One design of intra-ocular lens, fabricated from polymethylmethacrylate, utilizes a heparin surface coating in an effort to reduce inflammation. The evidence about performance is equivocal. It is clear that in high-risk patients, that is those with diabetes or a previous history of inflammatory disease, these lenses do reduce the risk of complications. Whether they do so in the patient population at large, however, is another question. The attachment of the heparin is not inexpensive. Budgets are limited and cataract surgeons have to decide whether to use standard or modified lenses. I was at a symposium on this subject recently and surgeons were divided as to the justification of using such lenses in all patients.

Let us pose this question; if you have a patient who had lost one eye through trauma a few years ago and then developed a cataract in the other eye, would you put in a more expensive lens simply because this eye was very important to him, or would you use the lower cost lens because there was no real evidence that this would pose any greater risk. An intriguing dilemma. If there was any statistical, actuarial evidence that the higher cost lens had a better chance of success, then cost should play no real part in the decision

because the cost of a higher number of failures could be far greater than the initial price differential.

The critical point was the availability of the evidence. Evidence of performance is hard to come by. Multicentre, statistically valid clinical trials are enormously expensive and difficult to coordinate, especially as with many procedures it takes a long time to assess the outcome. Last year a workshop was held under the auspices of DG XII of the European Commission in which representatives of many biomaterials and medical device companies in Europe were asked to discuss the constraints to innovation and the requirements of the industrial community with respect to the funding of basic and industrial research and development. By far the greatest plea was for assistance in the funding of clinical trials. It is only with appropriate, objective evidence that decisions such as the one I have described can be made. The costs of the extensive clinical trials have to be weighed against the financial returns a company can expect to make, and since the ultimate winners and losers are really the patients, the community, spelt either with a small or a large c, should contribute to the costs. Nationally or internationally organized registers or databases on medical device performance are also essential for the future in this respect.

Interestingly, while we all get concerned about the costs of regulatory approval, most companies at that workshop thought such procedures were a good thing and I feel that most people in the industry have no real fears in this direction. There may be one exception and that concerns the predictiveness of some biological test procedures, specifically those concerned with mutagenicity and carcinogenicity and I anticipate that major developments will take place in the near future to allow us to assess these risks more accurately.

There are, of course, many problems to overcome within Europe in the context of the implementation of the Medical Device Directives. For example, critical issues concerning the use of human and animal tissue derived material for use in medical devices need to be resolved. I can't help feeling that just as the BSE scare a few years ago had an impact on the use of bovine tissues, so the controversy in the media on the development of Creutzfeldt Jakob's disease in patients receiving Lyodura, involving human gonadotrophins derived from cadavers, will have some influence.

My final point here concerns the quality of surgical treatment. The receding horizon has, as one of it's most significant pinnacles, the late Professor Sir John Charnley and his original total hip replacement. I have heard it said many times during the last few turbulent years in orthopaedics that success rates now are not so high as they used to be. Charnley had his failures of course, indeed some patients died because of the unexpected pulmonary hypotension or fat embolism and most had to be recalled to have revision surgery because of the failure of the polytetrafluoroethylene. However, these mistakes were learnt while Charnley restricted the use of the prostheses to his own hospital.

After making considerable changes to both prosthesis and procedure, he still insisted that any surgeon who wished to use the device had to spend time at Wrightington learning the technique under his direction. Let us not forget that hip replacement is very technique sensitive and, without attacking at all current orthopaedic practices, it is clear that the surgeon who does not receive specialist training, preferably with instruction in biomechanics and biomaterials, and who does not specialize in arthroplasty but performs only the occasional case and who changes from one prosthesis to another with regularity, will not see the best results. Equally, we need to recognize that all surgeons, no matter how well trained and experienced, are not necessarily equal in ability.

Branemark demonstrated a similar outcome with dental implants and it is well known that the quality of anastomoses produced with small diameter vascular prostheses is crucial, as is the method of lens extraction in cataract surgery, of material placement in restorative dentistry and so on. I am, in brief, calling upon those who regulate and control the surgical and associated professions to recognize the special difficulties and challenges imposed by the use of implantable medical devices and arrange training pathways and clinical duties appropriately.

I have attempted, at what I believe is a critical time, to provide an accurate assessment of the situation and the risks. But I am the eternal optimist and would like to think that there are some large patches of blue sky ahead and a horizon that reflects some real hope.

I mentioned previously that we had made considerable progress in our understanding of biocompatibility and that we had a good array of structural biomaterials and interesting surfaces, and that the future may lie with the application of the science and practice of molecular biology to medical devices.

My views here should come as no surprise and I will not dwell upon the definition of biocompatibility nor the details of the associated phenomena.

It is, in my opinion, very clear that the materials science profession has provided us with an array of structural materials that can meet almost any intrinsic physical or mechanical performance we wish. There are a few notable exceptions, particularly wear resistance, but generally we have a wide range of materials to choose from when specifying properties such as elasticity, hardness, optical transparency, electrical conductivity, toughness and so on. It does not matter that these materials have not been designed for medical use and I do not side with those who complain that the medical profession does not have its own materials but rather has to borrow them from other applications.

This is not important. What is important is that the materials are able to continue to perform the function for which they have been selected, efficiently, effectively and safely, for the desired length of time, in that aggressive yet sensitive environment that is the human body. At the present it is clear that all materials show some deterioration in their properties and it is very difficult to meet the increased device life expectations. And that, after all, is what is meant by biocompatibility.

In the physical sciences, we are used to the concept of an activation energy, the energy required to over-

come a barrier beyond which a more stable, low energy state can exist. In biomaterials science, I regard the understanding of the mechanisms of biocompatibility as the barrier to the stable, low energy state of efficient usage of medical devices, for which we have an activation energy.

It has needed time, a combination of experimental work and clinical/pathological observation, the recognition that many of our ideas have been grossly in error, and the realization that biocompatibility is as much dependent upon the biological factors as the materials science, for us to gain a foothold on this path to understanding. We have been able, at the very least, to separate the search for materials that do no harm, from the search for materials that actually encourage or promote the desirable tissue reaction, hence the new concepts and definitions of biocompatibility. We have a far better understanding of how interfacial reactions are able to influence the long-term subtle changes that take place in both material and tissues, particularly with respect to the slow but remorseless attack on biomaterials by biological species and the involvement of intricate pathways of inflammation and tissue remodelling in the response to the presence of the materials. And now there is an appreciation of how cell–substrate interactions, specific reactions of recognition, attachment, activation and so on, at the cell-material surface junction can play vital roles.

What is the significance of this understanding? Why do we need to expend this activation energy?

I started with an analogy to the Davos environment and horizon. Whether in the snow of winter or the blue skies of summer, ignoring for a moment the sometimes ambivalent skies in between seasons, few could argue that this is a beautiful, near idyllic place.

Now imagine you were in a hypothetical adjacent land where, instead of beauty you had plainness, instead of serenity you had disquiet, instead of stability you had unrest. And if, between your land and Davos was a high range of mountains, and if you could guess what was on the other side, wouldn't you wish to expend the energy to climb that mountain and gain access to the utopia.

I believe the barrier to the more widespread successful use of medical devices, the high ridge obscuring the vision of our utopia, is our poor understanding of biocompatibility.

But having climbed a mountain, it is all very well to look down either at Davos, or at the perfect world of successful biomaterials performance. It is quite another thing to descend safely and thereby to reach our objective.

What I see as the crucial component of getting down, however, is the ability to use the **understanding** of biocompatibility in order to **achieve** biocompatibility. It may be that we can control events simply by doing what we have been trying to do for a long time but doing it better; that is trying to select materials that are inert when we want permanence or that are degradable when we want transience, but using our more detailed knowledge of the intricate mechanisms of physiological corrosion or degradation to make more sensible choices.

But, more importantly, I believe we will be designing substances that control biocompatibility through the inhibition of those events we do not want to occur and/or the stimulation of those events we wish to encourage.

Clearly the attachment of a wide variety of drugs or biologically active agents to polymer surfaces to control thrombosis, either through inhibitory effects associated with heparin or prostacyclin, or through the facilitation of endothelialization, provide us with good examples, but the future sees great potential in many areas of hard and soft tissue reconstruction and other therapies; particularly through the use of surfaces designed to interact with cell membrane receptors.

This must constitute the major vista of the blue skies of the biomaterial horizon. Such biological approaches may yield totally new materials; more likely they will yield either hybrid structures, incorporating traditional materials on new surfaces or appropriate mechanical substrates. Either way it will be a major challenge to integrate these surfaces and components into, or onto the structural devices, bearing in mind the aggressiveness of the tissue (enzymes, free radicals and cells) which can be so destructive of anything in its path.

Now the Swiss are an inventive people. After climbing a mountain in order to get to the other side, and finding a new valley or location they like, they devise ways of getting everybody there without the need for them all to climb the same mountains. And just as in electron physics we have tunnelling procedures to circumvent the activation energy of more major movements so the Swiss avoid the need for continual expenditure of activation energy of climbing by building tunnels.

It may be that at some time in the future we will have tunnels to take us from the challenging new concept in patient treatment, to the medical device solution, without the need to climb new mountains all the time, or especially to avoid the habit of climbing the old ones over and over again. Let us hope that there is truly a blue sky at the end of this tunnel **and** on the horizon, excluding the grey clouds by careful attention to the details of construction that I have outlined.

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