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Leading opinion

There is no such thing as a biocompatible material

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ABSTRACT

This Leading Opinion Paper discusses a very important matter concerning the use of a single word in biomaterials science. This might be considered as being solely concerned with semantics, but it has implications for the scientific rationale for biomaterials selection and the understanding of their performance. That word is the adjective 'biocompatible', which is often used to characterize a material property. It is argued here that biocompatibility is a perfectly acceptable term, but that it subsumes a variety of mechanisms of interaction between biomaterials and tissues or tissue components and can only be considered in the context of the characteristics of both the material and the biological host within which it placed. *De facto* it is a property of a system and not of a material. It follows that there can be no such thing as a biocompatible material. It is further argued that in those situations where it is considered important, or necessary, to use a descriptor of biocompatibility, as in a scientific paper, a regulatory submission or in a legal argument, the phrase 'intrinsically biocompatible system' would be the most appropriate. The rationale for this linguistic restraint is that far too often it has been assumed that some materials are 'universally biocompatible' on the basis of acceptable clinical performance in one situation, only for entirely unacceptable performance to ensue in quite different clinical circumstances.

1. Introduction

Biocompatibility is a subject that has been discussed and analyzed for over 50 years. However, the majority of the biomaterials community has spectacularly failed to understand the central biocompatibility paradigm. This is evidenced by the frequent use of the adjective 'biocompatible' to describe or categorize a biomaterial. There are some reports of superb experimental work with advanced biomaterials in the recent literature that fall foul of this basic misunderstanding, using expressions such as 'biocompatible quantum dots' and 'biocompatible (non-toxic) and cell adhesive tissue engineering scaffolds' in titles, abstracts and conclusions. Standards organizations, regulatory bodies and journals of the highest reputation and impact factors all do this. Authors of papers in this journal, *Biomaterials*, will be aware that whilst I have welcomed papers that discuss biocompatibility phenomena, I have never allowed the use of the adjective 'biocompatible' for well over 15 years.

This situation has been exaggerated in recent years in the transition of biomaterials science from a subject that was almost solely concerned with implantable medical devices to situations in which biomaterials are being used in gene and drug delivery processes, in cell therapy and tissue engineering and in a variety of imaging and diagnostic systems. These applications often involve materials at the nanoscale, which may be derived from bottom-up self-assembly, rather than monolithic materials manufactured by conventional top-down engineering. They may also come into contact with the human body by injection or within *in vitro* systems, so that the historical approach to biocompatibility as a perturbation to wound healing following surgical intervention cannot apply. Thus the definition of biomaterial has had to be extended and refined along the lines of 'A biomaterial is a substance that has been engineered to take a form which is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure' [1].

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In this article I shall explain the background to, and the seriousness of, the problem, and suggest ways in which our understanding of biocompatibility and its role in new clinical applications could be enhanced.

2. Biocompatibility as a characteristic of a material – biological host system and not a property of a material

We had an early indication of the problems of characterizing biomaterials on the basis of their putative biocompatibility with the *in vivo* performance of PTFE-based materials. Charnley, the inventor of metal-on-plastic hip replacements, first used a form of PTFE for the acetabular component of his devices on the basis of the low coefficient of friction and the chemical inertness of the material. In spite of the latter property, a massive local inflammatory response was seen in his first patients after a short time due to the fragmentation of the polymers and the host response to the particulates [2]. Time and time again since then, monolithic PTFE products have been tested and used clinically and found to pass all preclinical biological safety tests and for many people it is considered as a classic example of a 'biocompatible polymer'. Clearly, in spite of some excellent clinical applications, PTFE cannot be considered as a 'biocompatible material'. This becomes even more apparent when polymer surfaces are used in situations where cell adhesion to the surface is required, and indeed where that cell adhesion is the most critical event in the biocompatibility of that system; PTFE is well-known to be very hydrophobic and cells prefer not to attach themselves to the material unless it is profoundly surface modified, indicating that PTFE is far from 'biocompatible' in many such situations. Similar, if not so dramatic, situations can be found with other prominent biomaterials such as titanium, hydroxyapatite, cobalt–chromium alloys and silicone products.

The need to refer to the specific application when discussing biocompatibility has been recognized for a long time, reflected in the most widely used definition of biocompatibility as 'the ability of a material to perform with an appropriate host response in a specific application' [3]. The implication for the linguistic consequence of this definition, that the use of the word 'biocompatible' should be deprecated, is also accepted in principle, but, 25 years on, we are witnessing an expansion rather than a diminution of this misunderstanding and this use.

The fundamental situation is that the biocompatibility is a characteristic, and a complex characteristic at that, of a system and not a material. Knowing that a material may affect different biological systems in different ways, for example the tissue processes involved in wound healing, the target cells in gene therapy, the endothelium in contact with intravascular devices and the stem cells in bioreactors, makes it absolutely clear that there is no material with ubiquitous biocompatibility characteristics and no such things as a uniquely biocompatible material.

It should be noted here, of course, that interactions between biomaterials and tissues are time dependent and that some materials may be effectively conditioned after contact with the tissues, and this has to be taken into account in the characterization of the material – biological host system. It is also important to recognize that in many products of medical technology, more than one biomaterial may be involved and interactions between materials may play some role in biocompatibility.

3. The significance of understanding biocompatibility

So why does this matter? There are two related but somewhat different reasons. The first concerns material selection for new medical applications, and may be seen in the context of the lack of cell adhesion mentioned above. Let us take a synthetic polymer that is potentially useful for *ex vivo* tissue engineering applications. We normally require that this material should be fashioned in the form of a so-called scaffold, which should be porous so that cells could be seeded within it, and should be biodegradable so that it disappears while being displaced by the new tissue being generated by these cells. Virtually every tissue-engineering scaffold used in early systems utilized a synthetic polyester, such as polylactic acid or polycaprolactone, these materials having previously been used for medical devices such as sutures, plates and screws. Their biocompatibility was equated with the ability to be degraded without significant stimulation of inflammatory or immune systems. This is usually interpreted as the material being non-toxic. Having no negative effect on cells in culture, however, is rather different to having a positive effect on those cells in order to encourage them to express new tissue, through, for example, up-regulation of differentiation or proliferation events and facilitating appropriate gene expression [4]. In other words, the processes have now moved on from trying to ensure that the biomaterial does no harm to those where the material actively and synergistically interacts with cells so that they do good. These interactions may be controlled by surface energy, surface topography, surface functionality and substrate stiffness. The control of biocompatibility in tissue engineering situations involves, therefore, much more than non-toxicity, and to conclude that a scaffold has to be 'biocompatible' and show cell adhesion is obviously nonsense.

A similar situation arises with applications of nanostructured biomaterials in imaging and diagnostic systems. These include quantum dots, which have significant potential as powerful probes for fluorescence imaging, and polymeric and metal oxide based nanomaterials for gene and drug delivery and as contrast agents. If these systems, such as anti-HER2 quantum dot conjugates for imaging breast cancer cells, are used for laboratory diagnosis, questions of quantum dot toxicity do not really apply. As these and other complexes move towards *in vivo* use, however, significant issues arise with the overall biological performance of the nanoparticles. It is essential that the molecular design of the quantum dot ensures targeting to the appropriate cells, using, for example, conjugation with antibodies, peptides or small molecules [5]. In addition, many types of quantum dot are based on heavy metals such as cadmium, which usually have significant cytotoxicity, implying that rapid cell and whole body elimination has to be achieved. These factors mean that biocompatibility here incorporates a wide range of interactions, both chemically and biophysically based, with host systems that have to ensure good functionality and good safety. Clearly it is inappropriate to describe quantum dots as 'biocompatible' when there are so many potential interactions to consider. The same situation applies to nanoparticles used for the delivery of DNA to target cells, where endocytosis, intracellular transport, intranuclear release and the elimination of residues after payload delivery, are all essential contributors to the overall biocompatibility phenomenon [6].

The second, very practical, consequence of the misunderstanding of biocompatibility is the manner in which new biomaterials and new products are tested and qualified for human use. Worldwide, a standard series of tests for 'biological safety' are used by companies to establish the safety of their products. Many of these tests are long established, and even though they are totally inappropriate for these new systems, are still used for the benefit of regulatory approval [7]. Time and time again, submissions for regulatory approval provide evidence of the suitability of a biomaterial used in the construction of a product on the basis of apparently adequate performance in unrelated devices and different circumstances, and with new evidence of compliance with some very simple short-term toxicity and sensitization tests, with the often bizarre conclusion that the material has been shown to be