Titanium: epitome of biocompatibility or cause for concern

After three decades of total joint replacement, during which opinions have oscillated on fixation, design, and clinical technique, we are still faced with very difficult decisions about which materials should be used. While it is not surprising that difficulties and uncertainties arise with new materials, or with modifications of existing materials, it is strange that controversy still rages over some which have been in use for many years. Yet that has been and remains the case.

The sequence for materials such as polyethylene, acrylic cement, and cobalt alloys seems to be brief experimentation, gradual introduction to orthopaedic practice, widespread clinical use, general acceptance, then controversy. In particular, materials which have acquired a reputation for biocompatibility are often criticised at a later date for these same properties. Controversies about the tissue response to wear debris of the supposedly biocompatible polyethylene, or about the potential carcinogenicity of apparently inert metal alloys, demonstrate this point.

One current debate centres around the metal titanium. Experiments on the surgical use of this metal began more than 50 years ago and it has been used in orthopaedics since the mid-1960s. Commercially pure titanium became known as the most corrosion-resistant non-noble metal, a property which results from the inert oxide layer that spontaneously forms on its surface. It also became apparent that similar resistance to corrosion could be achieved by some titanium alloys, such as titanium-6% aluminium-4% vanadium, which had far superior mechanical strength (Williams 1982). Although corrosion resistance is a prerequisite for biocompatibility, it does not necessarily guarantee it; other properties of the metal are of crucial importance. The reputation of titanium as a 'biocompatible' material was based on its excellent corrosion resistance, which severely limits the amount of titanium ions released into the tissue under most circumstances, and on its biological inactivity, sometimes termed biological indifference, in that traces of the metal are not known to influence any part of the tissues.

Titanium gained its position within the hierarchy of biocompatibility in spite of the frequently observed gross discoloration of tissue near implants and the associated histological pigmentation. Studies made some 20 years ago clearly showed that the pigmentation was caused by titanium-bearing deposits, and trace-metal analysis confirmed the presence of the metal in spite of known corrosion resistance. It was also shown that this had little effect on tissue morphology and did not produce any clinically identifiable conditions (Meachim and Williams 1973).

What, then, is the problem? Why do recent papers refer to 'titanium metallosis' and 'titanium cysts' (Breen and Stoker 1993)? Why is 'biological indifference' now challenged by concepts of titanium immunogenicity (Lalor and Revell 1993), titanium-induced release of inflammatory mediators (Haynes et al 1993) and distant effects such as lymphadenopathy (Shinto et al 1993)? The probable answer is that, as with other instances of misplaced confidence in biocompatible materials, biocompatibility can refer only to the conditions under which it is measured and observed and can never be extrapolated to other conditions.

Biocompatibility should now be defined as "the ability of a material to perform, with an appropriate response, in a specific application" (Williams 1987). This implies that a material which has all the characteristics of biocompatibility under one set of conditions may show a different and possibly inappropriate response under different conditions. Experience with polytetrafluoroethylene illustrates this point. It is ostensibly the most inert of all polymers yet its early use in the Charnley hip replacement produced intense inflammatory reactions.

Even taking into account the fact that titanium is used in the form of an alloy, in which other components may be less innocuous than titanium itself, and that much more sophisticated methods are now available for the detection of subtle changes in host response, the early hypothesis that titanium was intrinsically biocompatible remains valid and indeed confirmed. Problems have arisen, however, when some of the less desirable aspects of titanium performance have either been unknown or underestimated. The most significant of these is the undoubtedly poor tribological properties of titanium and its alloys which have been known in orthopaedics for many years (Williams and Roaf 1973).

The wear rate for bearing surfaces in joint replacements has recently been discussed by Davidson (1993). He showed that the release rates of metal during sliding against polyethylene were in the ratio 1:2:10 for cobalt-chromium alloy: stainless steel: titanium alloy. The actual proportions vary a little from study to study, but it is generally agreed that titanium alloys wear more rapidly and also cause more polyethylene wear. Changes in alloy composition are unlikely to alter the situation significantly, and surface treatments such as nitriding or ion-implantation, although they have a marked initial effect, are also unlikely to improve radically the long-term performance (Milliano et al 1993). It may well be that

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increased wear, as well as producing significant and visually alarming pigmentation, may result in elevated serum titanium levels, although the toxicological and clinical significance of this is not clear. The number of reports of loosening of joint prostheses associated with extensive wear and tissue deposits of titanium make it hard to justify the continued use of titanium-bearing surfaces in total joint replacements.

It is not only the bearing surfaces which may abrade, however, and new controversy is likely to relate to the increased release of titanium from cementless femoral stems. When these become loose, fretting may release significant amounts of metal. Jacobs et al (1991) found that serum concentrations of titanium were raised in patients with loose titanium femoral stems. Titanium alloys have lower moduli of elasticity than other acceptable alloys, thus at least theoretically (if not necessarily practically) reducing micromotion between femoral stem and bone. This suggests that the material has a mechanical advantage, but that once loosening has occurred, abrasion will lead to more rather than to less metal release. It is often poorly understood that interfacial reactions in biocompatibility are themselves interdependent and autocatalytic. This must create thresholds below which failure cannot be predicted, but above which it is rapid and catastrophic. It is likely that titanium exemplifies this phenomenon, thus explaining its capricious behaviour.

We should always be aware that we do not fully understand the nature of the interactions between biomaterials and the body and that the hitherto unexpected may arise as we become more adept in examining the tissues that provide the response, and perhaps as we extend the range of situations in which we use the biomaterials. For many years titanium has been the non-immunogenic model, with no evidence that it could induce hypersensitivity, and with titanium compounds used as a base for preparations for the treatment of skin allergies. Recent observations by Lalor and Revell (1993), however, confirmed in our laboratory (Hunt et al 1994, in press), show that immunocytochemical staining methods make it possible to detect activated T-lymphocytes in association with accessory macrophages in the tissue around titanium-alloy orthopaedic implants, thus demonstrating an immunological response. Observations have also been made of the release of bone-resorbing mediators from macrophages, such as prostaglandin E2 and interleukin 1, in association with titanium wear debris (Haynes et al 1993). The significance of these observations is not clear but they are indicative of the need to maintain vigilance.

The current situation is that titanium is still an intrinsically safe biomaterial, and may be effectively used with minimal risk under many well-defined conditions. Outside these conditions, especially when large amounts of titanium are released as a result of enhanced wear, a critical level of reactivity may be reached within the tissues. Such reactions possibly involve mechanisms of which we are ignorant.

No material is universally 'biocompatible' and that includes titanium. Used appropriately, however, it can still provide a high level of performance and optimal behaviour.

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