A model for biocompatibility and its evaluation

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ABSTRACT

Concepts of biocompatibility have changed radically in recent years. This paper describes these new concepts and the present knowledge of the components and mediators of biocompatibility and leads to the development of a model for the explanation and rationalization of these phenomena. Of particular importance is the question of the assessment or evaluation of biocompatibility. The paper concludes with comments on the need for a schedule of biocompatibility assessment procedures to take into account this new thinking.

Keywords: Biocompatibility, assessment procedures

INTRODUCTION

The field of medical engineering has, among many other contributions to health care, provided the surgeon with a variety of implantable devices to be used in reconstructive surgery. Many of these examples are now commonplace and are highly successful. Indeed, procedures such as hip replacement and the treatment of cataracts with intraocular lenses may be numbered amongst today's most successful and rewarding surgical procedures. Their very success, however, hides the complexity of the issues involved. Other attempts to replace parts of the human body with synthetic engineering devices have not been so successful and this complexity has been only too plain to see. Replacement of small diameter arteries, skin and teeth demonstrate this point of view.

It is, perhaps, not too surprising that there are difficulties. Teleological arguments suggest that evolutionary processes have resulted in the highly efficient structures that comprise the human body and these are not likely to be replaced in their functional entirety by synthetic man-made structures. With most of today's implantable devices the tissues are replaced or augmented by structures that, at best, are able to supply a simple mechanical or physical function. In very few cases is a more complex biological function sought or obtained. The approach has been straightforward and has achieved both good and bad results. It has, however, basic limitations, both in terms of the longevity of the implants in question, because many eventually fail, and in terms of the next generation of implantable devices.

In this paper the nature of these limitations will be explored. The most fundamental point which has to be addressed is that reconstructive surgery using implants has historically been based on the hypothesis, or perhaps unchallenged assumption, that to interface a synthetic material with the tissues of the body must demand inertness from the material. This is consistent with the desire to achieve simple mechanical or physical function and implies that the more inert the material, the more tolerant will be the body to that material.

This, however, may be an intellectual cul-de-sac which cannot lead to sophisticated multifunctional long term implants. This inertness, which has led to the widespread use of stainless steel, cobalt-chromium alloys, polytetrafluoroethylene, alumina and polymethylmethacrylate, implies a minimum interfacial reaction. This itself, however, implies a tolerance rather than an acceptance, a passive ignorance rather than an active recognition. No device placed within the body can be considered truly incorporated within it if it is ignored. It is clear from many experiences, including loosening of the otherwise successful hip replacements, that long term success is dependent upon adequate incorporation. This requires active biological incorporation.

This argument is reinforced by the knowledge that there is no such thing as absolute inertness in the very hostile physiological environment. Therefore, the goal of benign tolerance is itself questionable. If the performance of a prosthesis in the long term is dependent on continued inertness, then an eventual manifestation of an interfacial reaction is likely to lead to failure by one of several mechanisms.

These two issues, the need for biological incorporation and the improbability of complete and acceptable inertness, are central to the new thinking about biocompatibility. It is argued here that biocompatibility is the key to improved performance and extended capabilities in prostheses for reconstructive surgery, or indeed, for any implantable device.
CONCEPTS OF BIOCOMPATIBILITY

Biocompatibility is a word which has been used by many different people in the past to mean many different things. It concerns the relationship between a biomaterial and its host. The traditional view of inertness usually implies that biocompatibility has to be equated with a lack of toxicity. The difficulties with this concept have now led to a different perspective on the subject. The term has recently been defined as "the ability of a material to perform with an appropriate host response in a specific application." Biocompatibility is concerned with all aspects of the interfacial reaction between a material and the tissues of the body but concentrates, as the focal point, on the appropriate host response. The host response is the reaction of the tissues to the implant and it controls the physiological performance of the patient following placement of the implant. It should be noted that the definition refers to an active rather than a passive role of the implant by use of the words "ability" and "perform", and refers to different situations by involving appropriateness in the light of these situations. The definition allows for complete inertness, should that be desirable or attainable, but equally allows for specific biological (or pharmaceutical, if necessary) activity to produce a specific desirable response. It is important to note that biocompatibility has to refer to a specific situation. The biocompatibility characteristics of a material in one situation may be quite different to those in another. A consequence of this concept is that, whilst biocompatibility is an acceptable term to describe a phenomenon, or set of characteristics, there can be no justification of using the term biocompatible as an adjective to describe a material.

It is usual to identify four components of biocompatibility:

1. The initial events that take place at the interface, mainly including the adsorption of constituents of tissue fluids onto the material surface.
2. Changes in the material as a result of its presence in the tissues, usually described under the headings of corrosion or degradation.
3. The effects that the material has on the tissue, the local host response.
4. The sequelae of the interfacial reaction that are seen systemically or at some remote site.

These four sets of phenomena may be treated independently, and indeed, because the mechanisms and principles may be so different, it is often convenient to do so. On the other hand, they are all inter-related and dependent upon each other, so that it is equally logical to consider them together. It is known, for example, that the corrosion of metals is influenced by both pH and oxygen potential. Because the presence of an implant in tissues can induce changes that, on a very localized and microscopic scale, are concerned with such variables, the rate and the mechanism, of corrosion may vary. However, as the rate of corrosion varies the tissue response may change, because it will be influenced by the released corrosion products. Both processes are, therefore, dependent on each other and it is sensible to consider biocompatibility as a single complex phenomenon, with many interrelated contributing factors.

With this in mind, let us consider the variables which are likely to influence biocompatibility. These can be grouped into three areas, the material variables, the host variables, and system variables.

As far as the material itself is concerned, naturally its chemical nature is an important factor, both in relation to bulk and surface chemistry. Any heterogeneity of this structure has to be taken into account, because critical events in interfacial reactions may well be controlled at a microstructural level by minor constituents such as grain boundaries, precipitates or impurities. In addition to the chemistry and structure, the surface topography is also important. At the extremes there will obviously be significant differences in both material stability and cellular responses between ultra smooth surfaces and porous structures. Between these extremes it is reasonable to assume that variations in surface roughness will control many of the parameters of biocompatibility.

Material variables have traditionally been considered the most relevant in biocompatibility studies, but it is now becoming clear that host variables can be equally relevant. The local host response represents a balance between inflammatory and repair processes. There are many mediators of inflammation, each influenced by a wide spectrum of physiological and pharmaceutical variables. In the context of the clinical situation, the age, sex, state of health and pharmacological status will also influence these processes and, of course, we should expect variations from site to site within the body. Perhaps even more importantly, when trying to assess biocompatibility characteristics from animal experiments, there will inevitably be species differences. As noted in more detail below, however, the nature of these differences and their precise causes are far from clear.

By system variables is meant those features which relate to the tissue-implant complex. These include the stress system within this complex and its influence on tissue, especially in relation to altered load distribution within the tissue. This is often referred to as biochemical compatibility.

With these ideas about the nature of biocompatibility, its components and mediators, it is possible to develop a model for biocompatibility and use it in improving knowledge of biocompatibility and determining procedures for its evaluation. Here a model of the local host response is presented as a first step in the process. A more detailed version of this model is being published elsewhere.

THE MODEL OF BIOCOMPATIBILITY

Consider a volume of connective tissue of unspecified nature and location. If this tissue is damaged in some way, there is a well-defined mechanism by which healing will attempt to take place. This mechanism involves two phases, distinct in function but overlapping in time. The first phase is that of inflammation, the initial reaction of the body to injury that involves localized changes to the microvasculature and cellu-
lar composition of the tissue. The second is the repair phase in which the tissue attempts to restore, structurally and if possible functionally, the damage.

The process itself is depicted diagrammatically in Figure 1. A volume of tissue is described in which the boundaries are arbitrary and not associated with any specified interface. In Figure 1a the tissue has been injured. This is represented by a clean incision that completely traverses the volume. The immediate response to this injury is bleeding from the severed blood vessels and the formation of a clot, involving especially the formation of fibrin, the activation of platelets and the entrapment of red blood cells. Very quickly the vessels in the immediate vicinity dilate and allow the diffusion through their walls of white blood cells, especially neutrophils, and an extracellular exudate which contains plasma proteins and mediators of the biochemical reactions which are to follow, especially serotonin and histamine. This phase, depicted in Figure 1b, is the acute inflammatory reaction. The cells of this reaction are primarily involved in attending to the injury and removing debris. Those cells with phagocytic activity, for example, in particular macrophages, ingest cellular and other debris.

Concomitantly with this activity (Figure 1c) is the start of vascular regeneration, as new capillaries grow into the wound area, and the beginning of the repair process, in which the fibroblasts, both pre-existing and newly arrived, lay down new collagen, the essential structural protein of this connective tissue. Eventually the inflammatory process succeeds in combating the injury and removing the debris and the repair process succeeds in re-establishing continuity. The result is the formation of a layer of fibrous connective scar tissue (Figure 1d). In very simple cases this may differ only slightly from the original connective tissue it has replaced. The response is a sequence of inflammation and repair. It is the balance between inflammation and repair, itself dependent on the magnitude of the injury, that controls the eventual outcome, including the time it takes for resolution. A more extensive injury will necessitate a more extensive inflammatory response, which will both delay the resolution of the repair phase and increase the quantity of reparative scar tissue that eventually forms.

These arguments apply to any transient injury in which the inflammatory process occurs subsequent to the injury and, of necessity, follows removal of the source of the injury (i.e. removal of the surgeon's knife, etc.). If the cause of the irritation is not

![Figure 1](image-url)

**Figure 1** a. Volume of tissue, traversed by a clean incisional wound; b, the acute inflammatory response, involving dilation of blood vessels and infiltration of cells; c, macrophages of the inflammatory response together with fibroblasts and new collagen; d, later stages of repair with fibrous scar tissue, reconstituted vascularity and low level of cellularity.
removed, the inflammation has to take place in its continued presence. In the case of a bacterially derived lesion, the bacteria will still be present some time after the inflammatory process has been initiated. The phagocytic cells of the inflammatory process effect the removal of the bacteria. With a non-organic foreign body such as an implant, however, it is highly unlikely that the defence mechanism will be able to deal with the invader so effectively. The consequence is that the implant acts as a persistent, and usually immovable, source for irritation. This persistence inhibits the inflammatory and repair processes. It is in this light that the perturbation to the wound healing as a basis for the model of biocompatibility is considered here.

There are many cells and chemical mediators that constitute the response to trauma and irritation in the tissue. There are, therefore, many points at which the normal sequence may be modified by variations in the nature of the irritant. Although the same mechanisms exist whatever the irritant, different components of the response may take on greater

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**Figure 2** a, Volume of tissue, traversed by clean wound containing a monolithic solid implant. b, immediate filling of area by blood; plasma proteins adsorb onto implant. c, acute inflammatory response; d, repair process results in collagenous capsule starting to form; e, fibrous scar tissue and capsule around implant.
or lesser significance with variations in the conditions.

In the case of a monolithic solid implanted in the wound (Figure 2a), consisting of a single material that is neither toxic to the host (in the normal sense of that word) nor overtly degraded by the tissues, the inflammatory response may take place virtually unaffected. The site of implantation fills with blood and a fibrin network forms a basis for subsequent fibrous tissue growth to occur. There is an initial interaction between the blood and the implant (Figure 2b), with plasma proteins being adsorbed on the implant surface. An acute inflammatory response is initiated (Figure 2c) and it is unlikely that the exudate will be different to that produced by the incision in the absence of the implant. Macrophages take over from the neutrophils fairly rapidly, as before. Capillary buds migrate through the clot but their passage across the wound is disrupted by the implant and the blood vessel network will inevitably be different.

Fibroblasts also become active and lay down collagen as the fibrin clot is resorbed. However, this will not be able to traverse the incision in the region of the implant, resulting in an altered morphology (Figure 2d). It is probable that the presence of the implant will prolong the inflammation and repair processes and the cellular infiltration will persist for a longer time than in the normal incisional case. Within 4–6 weeks, however, the tissue response should have stabilized, leaving a zone of tissue that is rather similar to the normal scar tissue, with perhaps differing patterns of vasculature and collagen fibres running parallel to the implant surface (Figure 2e).

However, this response is rarely seen. It is often described as a classical fibrous encapsulation of implants but this term is too simplistic. Absolute inertness of a biomaterial is rare and other material and device characteristics can be superimposed on inertness to modify this response. Of the currently used biomaterials, pure titanium, high purity alumina and some special grades of polymers such as polyethylene, may elicit this minimal fibrous capsule under some conditions.

It has historically been assumed that this minimal fibrosis is the ideal response, but this is not necessarily so. Any implant which is effectively ignored by the body in this way cannot be considered as being truly incorporated in it, a pre-requisite, of a successful, functional device.

If we consider some chemical reaction between implant and tissue takes place, then we may have the situation where there is no overtly detectable change to the implant but where some reaction products, almost certainly soluble, will be released into the tissues. It is unlikely that the initial events will be significantly altered in the development of the host response, but it is possible that small but subtle effects will be seen on the mediators of inflammation and the subsequent cellular activity. It may be that the characteristics of the extracellular exudate will be slightly modified, with perhaps minor influences on the chemotactic attraction of cells, a slightly greater stimulus to phagocytosis by macrophages and so on. The end result will depend, to a considerable extent, on the ability of the products to influence biochemical events and the ability of the local tissues to transport them away from the site. If some equilibrium is reached where the rate of release into the tissue is equalled by the rate of removal, a steady state may be achieved, probably accompanied by minimal inflammatory cells, and a greater degree of fibrosis associated with the stimulus to fibroblastic activity (Figure 3a).

With a more significant interfacial reaction it may not be possible to reach a steady state. Thus an accumulation of products, perhaps precipitated as an organic complex, may result. If these products are minimally active biologically, then they may be accommodated without a significantly greater cellular response, or any clinically recognizable symptoms (Figure 3b). If there is greater biological activity, the host response will increase, especially with an exacerbation of the chronic inflammatory response and a delay to the repair process. The result may be a persistent mild chronic inflammation, which is never fully resolved and where repair is never complete (Figure 3c).

The rate of reaction may not be linear, and it is here that the interplay between the effects of materials on tissues and vice versa can be seen. Because of the process of passivation it is quite likely that interfacial reactions may be stifled or reduced by surface oxidation or adsorption processes. Equally, the collagenous capsule that forms during the attempt at repair may alter the micro-environment and reduce susceptibility. On the other hand, adsorbed proteins may accelerate the corrosion of some metals. The lysosomal enzymes released from the cells of the inflammatory response are known to influence the degradation of some polymers. If the initial rate of reaction is low, but then increases, perhaps with the later release of more overt degradation products and significant destruction to the implant, then a later development of the chronic inflammation will be seen. A collagenous capsule may have already developed and the infiltration of inflammatory cells may have to take place subsequent to, rather than before, this process. This will obviously lead to differences in cell mobility and degradation product mobility. It is likely that a very extensive localized reaction may occur.

If degradation products are difficult to remove, then the cellular response may be directed towards their breakdown. Phagocytic cells, especially macrophages, will attempt to ingest any debris. However, because the debris will often be indigestible to these cells due to their inorganic nature, the process of elimination is not so straightforward. In particular, the macrophages will become highly activated in their attempts to digest the debris and will synthesize and release large quantities of lysosomal enzymes. Once extracellular, these enzymes may be both destructive and chemotactic. They may result in the attraction of a greater number of cells and tissue damage. This, in itself, prolongs and exacerbates both inflammation and repair. The resulting situation is often referred to as a 'foreign body reaction'. Technically this tissue response may be described as a granuloma. The more extensive tissue reaction,
involving more active biological species, may itself promote and accelerate further degradation, so that the process is autocatalytic (Figure 3d).

THE RELEVANCE TO NEW CONCEPTS OF BIOCOMPATIBILITY

It is important to visualize the biocompatibility phenomena in terms of such a model in order to judge and measure the influence of variables and exercise control over the process. This is, perhaps, the most important factor, because biocompatibility has traditionally been considered as a series of events which may be observed rather than a sequence which may be controlled. This model is still, perhaps, a little simplistic because it refers to one type of connective tissue only, but it does allow us to consider what may happen when the conditions are varied.

The model may be used, for example, to describe the sequence of events leading to bone bonding, with the so-called bioactive glasses and ceramics. The concept of biological control over the interfacial reaction is well demonstrated by this facet of bioactivity, which is concerned with the need to produce a stable structural bond between materials and bone\(^{10}\). This is relevant to both orthopaedic and maxillofacial implants. If a recipient bed is prepared in bone, and a material placed within it, there is a natural tendency, according to the mechanisms of this model, for fibrous encapsulation to take place. This, however, is not necessarily the appropriate response, because a soft intervening layer between bone and implant will not lead to rigid incorporation. Where such rigid incorporation is desirable it is necessary for bone instead of fibrous tissue to be formed. This will happen if, and only if, the fibrosis is inhibited and osteogenesis enhanced at this inter-

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**Figure 3** a. Fibrous capsule forming around implant of minimal reactivity. The capsule is thicker and/or denser than that of Figure 2e. b. Slightly greater reactivity, with observable reaction products in the tissue and evidence of some surface disruption. c, involving more active biological species, may itself promote and accelerate further degradation, so that the process is autocatalytic (Figure 3d). d. Even greater reactivity, leading to chronic inflammation and repair process, which may never be resolved. d, Mutual interaction between surface degradation and chronic cellular response.
face. In the practical case this may be a matter of relative kinetics with, effectively, post-inflammation fibrosis competing with osteoinduction or osteoconduction at the interface. The argument may be taken a little further by considering those situations where a specific fibrous interface would be useful, for example, forming a pseudo-periodontal membrane in an endosseous dental implant. It is not clear at this stage what features could be controlled in order to produce the proper blend of collagen orientation and fibre attachment to achieve such a functioning membrane. However, an improving understanding of biocompatibility will eventually allow this.

This is only one example of the relevance of a model of biocompatibility to the understanding of the way in which clinical performance is dependent upon the features of these interfacial reactions. Other areas which may be cited include the attempts to control the long term fate of pacemaker electrodes in respect of rising stimulation thresholds and membrane. However, an improving understanding of biocompatibility which are no more than crude toxicity tests. Acute systemic toxicity tests cannot be indicators of biocompatibility. It is, therefore, necessary to develop new test procedures for the assessment of biocompatibility. There will not be one single test method because the reactions are numerous and complex, so a schedule has to be determined. This will inevitably have to involve both in vitro and in vivo procedures. Both types have their advantages and disadvantages. In vitro tests can be made to be reproducible and are especially suitable for measuring the effects of changing one variable at a time. They are, however, difficult to correlate with clinical performance. In vivo test procedures should be more relevant but there are still unanswered questions about species differences and the role of all the host variables mentioned earlier. It is an unfortunate situation that much of our knowledge of biocompatibility has been obtained from experiments on young, healthy, drug-free rats, whereas most implants (apart from cosmetic implants) are used in older humans who, by definition, are not so healthy and who are often recipients of a selection of drugs.

The answers to these dilemmas are not clear. Whatever test procedures are chosen, they should reflect the nature of the critical components of the biocompatibility phenomenon. They should address both biomechanical and morphological aspects of the reactions and should be quantitative as well as qualitative. There is no doubt that the use of image analysis based histomorphometry will supersede subjective scoring as a basis for describing the cellular response to materials, and the use of state-of-the-art radioimmunoassays and biochemical assays will play significant parts in the detailed assessment of these reactions.

**CONCLUSIONS**

It has become increasingly obvious that synthetic engineering materials cannot be placed within the body with impunity. There is no such thing as ‘biinertness’ as far as implants are concerned. The definition of biocompatibility expressed in this review is, at last, allowing for the recognition that the events which take place at the interface are complex, multiple and inter-related. The model for biocompatibility expressed here, its future refinement and the consequent development of a portfolio of relevant and quantifiable test procedures should all lead to an understanding of what is required for improved performance of implantable devices.

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