Biomaterials xxx (2008) 1–13

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Leading Opinion

On the mechanisms of biocompatibility☆

David F. Williams [a,b,c,d,*]

[a] Emeritus Professor, University of Liverpool, UK
[b] Visiting Professor, Christiaan Barnard Department of Cardiothoracic Surgery, University of Cape Town, South Africa
[c] Visiting Professorial Fellow, Graduate School of Biomedical Engineering, University of New South Wales, Australia
[d] Guest Professor, Tsinghua University, Beijing, China

ARTICLE INFO

Article history:
Received 17 March 2008
Accepted 11 April 2008
Available online xxx

Keywords:
Foreign body response
Inflammation
Implant
Scaffold
Biodegradation

ABSTRACT

The manner in which a mutually acceptable co-existence of biomaterials and tissues is developed and sustained has been the focus of attention in biomaterials science for many years, and forms the foundation of the subject of biocompatibility. There are many ways in which materials and tissues can be brought into contact such that this co-existence may be compromised, and the search for biomaterials that are able to provide for the best performance in devices has been based upon the understanding of all the interactions within biocompatibility phenomena. Our understanding of the mechanisms of biocompatibility has been restricted whilst the focus of attention has been long-term implantable devices. In this paper, over 50 years of experience with such devices is analysed and it is shown that, in the vast majority of circumstances, the sole requirement for biocompatibility in a medical device intended for long-term contact with the tissues of the human body is that the material shall do no harm to those tissues, achieved through chemical and biological inertness. Rarely has an attempt to introduce biological activity into a biomaterial been clinically successful in these applications. This essay then turns its attention to the use of biomaterials in tissue engineering, sophisticated cell, drug and gene delivery systems and applications in biotechnology, and shows that here the need for specific and direct interactions between biomaterials and tissue components has become necessary, and with this a new paradigm for biocompatibility has emerged. It is believed that once the need for this change is recognised, so our understanding of the mechanisms of biocompatibility will markedly improve.

1. Introduction

The single most important factor that distinguishes a biomaterial from any other material is its ability to exist in contact with tissues of the human body without causing an unacceptable degree of harm to that body. The manner in which the mutually acceptable co-existence of biomaterials and tissues is developed and sustained has been of interest to biomaterials scientists and users of medical devices for many years. It has become clear that there are very many different ways in which materials and tissues can interact such that this co-existence may be compromised, and the search for biomaterials that are able to provide for the best performance in devices has been based upon the acquisition of knowledge and understanding about these interactions. These are usually discussed in the broad context of the subject of biocompatibility.

Biocompatibility is a word that is used extensively within biomaterials science, but there still exists a great deal of uncertainty about what it actually means and about the mechanisms that are subsumed within the phenomena that collectively constitute biocompatibility. As biomaterials are being used in increasingly diverse and complex situations, with applications now involving tissue engineering, invasive sensors, drug delivery and gene transfection systems, the medically oriented nanotechnologies and biotechnology in general, as well as the longer established implantable medical devices, this uncertainty over the mechanisms of, and conditions for, biocompatibility is becoming a serious impediment to the development of these new techniques. This review of biocompatibility attempts to address some of these uncertainties

☆ *Editor's Note*: This Leading Opinion Paper is based upon a series of presentations given by the author at the University of Washington Summer Workshop in August 2003, a keynote paper at the World Biomaterials Conference in Sydney, 2004, the Gordon Research Conference on Biomaterials, Biocompatibility and Tissue Engineering, New Hampshire, USA in 2005, the Ratner Symposium in Maui, 2006 and the Founders Award Presentation, Chicago, 2007. It forms the first of a series of essays that will be published, in different journals, on the subjects of the principles of biomaterials' selection. Since the author is Editor-in-Chief of the journal, the paper has been refereed by four of the Associate Editors and revised on the basis of their reports. The opinions expressed in the review are, however, the sole responsibility of the author. It should also be noted that the reference list cannot represent the totality of literature on biocompatibility but points to some of the more significant literature that reflect the clinical outcomes concerned with biocompatibility.

* Ave de la Foret 103, Brussels, B-1000, Belgium.
E-mail address: dfw@liv.ac.uk

0142-9612/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biomaterials.2008.04.023

and provides a proposal for a unified theory of biocompatibility mechanisms.

2. The evolution of current concepts of biocompatibility

Biocompatibility has traditionally been concerned with implantable devices that have been intended to remain within an individual for a long time. To those who were developing and using the first generation of implantable devices, during the years between 1940 and 1980, it was becoming increasingly obvious that the best performance biologically would be achieved with materials that were the least reactive chemically. Thus, within metallic systems the plain carbon and vanadium steels, which demonstrated overt corrosion, were replaced by increasingly superior stainless steels, then by the strongly passivated cobalt–chromium alloys, titanium alloys and the platinum group metals. With polymers, the readily available and versatile nylons and polyesters were replaced by the more degradation resistant PTFE, PMMA, polyethylene and silicones. Consistent with this approach, the selection criteria for implantable biomaterials evolved as a list of events that had to be avoided, most of these originating from those events associated with the release of some products of corrosion or degradation, or additives to or contaminants of the main constituents of the biomaterial, and their subsequent biological activity, either locally or systemically. Materials were therefore selected, or occasionally developed, on the basis that they would be non-toxic, non-immunogenic, non-thrombogenic, non-carcinogenic, non-irritant and so on, such a list of negatives becoming, by default, the definition of biocompatibility.

Three factors initiated a re-evaluation of this position. The first was that it became obvious that the response to specific individual materials could vary from one application site to another. Thus biocompatibility could not solely be dependent on the material characteristics but also had to be defined by the situation in which the material is used. Secondly, an increasing number of applications required that the material should specifically react with the tissues rather than be ignored by them, as required in the case of an inert material. Thirdly, and in a similar context, some applications required that the material should degrade over time in the body rather than remain indefinitely.

It was therefore considered that the very basic edict that biocompatibility, which was equated with biological safety, meant that the material should do no harm to the patient, was no longer a sufficient pre-requisite. Accordingly, biocompatibility was redefined in 1987 as follows:

> *Biocompatibility refers to the ability of a material to perform with an appropriate host response in a specific situation* [1].

This definition, which clearly places the word in the category of a concept rather than a practical descriptor of a process, is based on the three tenets that a material has to perform and not simply exist in the tissues, that the response which it evokes has to be appropriate for the application, and that the nature of the response to a specific material and its appropriateness may vary from one situation to another [2].

It could be argued that this definition is so general and so self-evident that it is not of any real help in advancing knowledge of biocompatibility, and indeed it is true that it has not led to a greater understanding of specific mechanisms and individual processes, or to the innovation of new biomaterials. Moreover, it is likely that one concept cannot apply to all material–tissue interactions that pertain to widely varying applications, ranging from a drug eluting stent to a tissue engineering cartilage construct, a joint replacement prosthesis or an invasive biosensor. It is with this diversity in mind, and the wide ranging potential mechanisms of interactions based both on materials science and on biology, that a different paradigm of biocompatibility can be devised. We do so here with reference to the evidence that has accumulated over the last 50 years through experiment and clinical experience.

3. The agents of biocompatibility

The paradigm of biocompatibility outlined in this paper involves the separate, but potentially interrelated, responses of the two phases of the biomaterial–tissue complex and the interfacial phenomena that come into play when they meet. Probably the most important underlying principle is that the mechanisms by which materials and human tissues respond to each other are not unique to this particular use but are merely variations of natural processes that occur within materials and biological sciences. Thus, in general, the response of a material to implantation in the human body will not involve totally new mechanisms not found in other environments, and the cellular and humoral responses of the body do not involve the cellular and extracellular constituents performing in ways which are entirely non-physiological. The key to understand biocompatibility is the determination of which chemical, biochemical, physiological, physical or other mechanisms become operative, (and why), under the highly specific conditions associated with contact between biomaterials and the tissues of the body, and what are the consequences of these interactions.

Before discussing these mechanisms and the various causal relationships in biocompatibility, it is worth noting that there are several mediators of the biocompatibility of a material other than the material itself. Of great significance is the nature and quality of the clinical intervention that places the material into contact with the tissues. For implantable medical devices, the characteristics of the individual in or on whom the device is placed are also of considerable importance and it is to be anticipated that wide patient-to-patient variability will be seen. Age, sex, general health and concurrent disease, physical mobility, lifestyle features and pharmacological status all contribute to this variation [3]. The design of the device and the physical relationship between the device and the body play significant roles [4], as do the presence or absence of micro-organisms [5] and endotoxins [6]. This review concentrates on the material-derived processes but these always have to be considered in the context of the totality of biocompatibility.

In Table 1, the major material characteristics that may conceivably influence the host response are listed. These can be divided into characteristics of the bulk material and those of the surface. The majority of these characteristics are self-evident although obviously some subsume a number of features. The elastic constants, for example, include Young's modulus, shear and bulk moduli and Poisson's ratio. Crystallinity in polymers includes the degree of crystallinity and the nature of the molecular symmetry, whilst in metals it includes crystal structure, preferred orientations and grain size.

Table 1
Major material variables that could influence the host response

Bulk material composition, micro- (or nano)-structure, morphology
Crystallinity and crystallography
Elastic constants
Water content, hydrophobic–hydrophilic balance
Macro-, micro-, nano-porosity
Surface chemical composition, chemical gradients, surface molecular mobility
Surface topography
Surface energy
Surface electrical/electronic properties
Corrosion parameters, ion release profile, metal ion toxicity (for metallic materials)
Degradation profile, degradation product form and toxicity (for polymeric materials)
Leachables, additives, catalysts, contaminants and their toxicity (for polymeric materials)
Dissolution/degradation profile, degradation product toxicity (for ceramic materials)
Wear debris release profile

Please cite this article in press as: David F. Williams, On the mechanisms of biocompatibility, Biomaterials (2008), doi:10.1016/j.biomaterials.2008.04.023

Table 2
Major characteristics of the generic host response to biomaterials

Protein adsorption and desorption characteristics
Generalised cytotoxic effects
Neutrophil activation
Macrophage activation, foreign body giant cell production, granulation tissue formation
Fibroblast behaviour and fibrosis
Microvascular changes
Tissue/organ specific cell responses (e.g. osteoclasts and osteoblasts for bone, endothelial proliferation)
Activation of clotting cascade
Platelet adhesion, activation, aggregation
Complement activation
Antibody production, immune cell responses
Acute hypersensitivity/anaphylaxis
Delayed hypersensitivity
Mutagenic responses, genotoxicity
Reproductive toxicity
Tumour formation

Table 3
State-of-the-art in materials' selection for long-term implantable devices

Material	Applications
Titanium alloys	Dental implants, femoral stems, pacemaker cans, heart valves, fracture plates, spinal cages
Cobalt–chromium alloys	Bearing surfaces, heart valves, stents, pacemaker leads
Platinum group alloys	Electrodes
Nitinol	Shape memory applications
Stainless steel	Stents, orthopaedic implants
Alumina	Bearing surfaces
Calcium phosphates	Bioactive surfaces, bone substitutes
Carbon	Heart valves
UHMW polyethylene	Bearing surfaces
PEEK	Spinal cages
PMMA	Bone cement, intraocular lenses
Silicones	Soft tissue augmentation, insulating leads, ophthalmological devices
Polyurethane	Pacemaker lead insulation
Expanded PTFE	Vascular grafts, heart valves
Polyester textile	Vascular grafts, heart valves
SIBS[a]	Drug eluting stent coating

[a] Poly(styrene-*block*-isobutylene-*block*-styrene) [135].

When placed in or on the tissues of the body, a number of reactions to a material may be seen over time, and these are listed in Table 2. Some of these, as examined later, may constitute important determinants of the host response, whilst others are of greater importance in the functioning of the device. Within the host, in the majority of circumstances, we may envisage a sequence of events, potentially involving the interaction between proteins and other physiological macromolecules with the material surface, the initiation of inflammatory and/or immune responses, and then the repair and/or regeneration processes that may lead to stable equilibrium between material and host. This is the classical biocompatibility paradigm that has been discussed in one form or another over the last couple of decades [7].

In determining the actual significance of each potential agent of biocompatibility, and how they are able to control the individual features of the sequence outlined in this simple paradigm, we may discuss some of the situations in which materials come into contact with human tissues and consider the evidence concerning the mediation of biocompatibility in these situations. The purpose of this essay is to develop a more comprehensive paradigm of biocompatibility using the examples of long-term implantable devices, intentionally degradable implantable systems, intravascularly invasive short term medical devices and tissue engineering products.

4. The long-term implantable medical device

Recognising that the most trusted data on the biocompatibility of a material must come from the actual use of that material in practical clinical examples in humans, we shall review first the generic evidence concerning some well known clinical procedures, taken from a spectrum of conditions involving both hard and soft tissues and blood contact. It is noted, of course, that data on many devices may not always be definitive with respect to materials since more than one material may be involved in a device, and since other factors, for example biomechanical and haemodynamic factors, may well be as important as the material characteristics, but it is relatively straightforward to establish the main features of clinical biocompatibility. All of the examples in this section involve devices that are intended for long-term performance for the replacement of damaged or diseased tissues. Table 3 summarises the state-of-the-art in materials' selection for such devices.

4.1. Total joint replacement prostheses

The biomaterial requirements of total joint replacements have become clearer over the 40 years since their first introduction, being aimed at maximising relevant mechanical properties (including fatigue strength, creep strength, toughness and wear resistance), minimising material deterioration (including corrosion, degradation and wear resistance) and facilitating long-term incorporation of the device into the musculoskeletal system (involving, for example, either cements or bioactivity). Specifically in relation to biocompatibility, the materials are required to optimise the rate and quality of bone apposition to them, to minimise the rate of release of corrosion or degradation products and the tissue response to them, to minimise the rate of wear debris release and the tissue response to this debris, and to optimise the biomechanical environment in order to minimise disturbance to homeostasis in the bone and surrounding soft tissue. Experience has shown that the optimal balance of mechanical properties with metallic components is best achieved with either titanium alloys or cobalt–chromium based alloys and no generalised biocompatibility advantage has ever been achieved outside of these alloys or through modifications within the specifications of these alloys, including surface modifications. In spite of many claims to the contrary, there are no specific biocompatibility characteristics that are dependent on the alloying elements in titanium alloys, nor, with the exceptions of idiosyncratic hypersensitivity responses, on the precise composition of cobalt–chromium alloys. The only characteristic that controls the host response to these alloys is the rate of metal ion release. When these alloys are placed, un-cemented, in direct contact with bone, the precise chemical composition within each group does not influence the eventual strength of attachment to the bone, nor, to any clinically significant extent, the rate of bone apposition. Titanium alloys do give better and faster attachment to bone than cobalt–chromium alloys [8], but the precise surface chemistry does not appear to make any difference [9]. This is in contrast to the surface texture, where surface roughness and/or porosity does influence the response of the bone [9,10]. There is evidence that some metallic elements, particularly nickel, can stimulate the immune system [11].

With respect to polymers, again the critical factor in biocompatibility is the balance of mechanical properties and degradation resistance, and the issues of polyethylene wear debris have been widely discussed. The precise mechanisms of particle-induced osteolysis have perhaps not been fully resolved with respect to the interplay between inflammatory cells and the osteoblast–osteoclast relationship, but the overall situation is clear [12]. As wear debris is released, inflammatory cells, most significantly macrophages and giant cells, respond and, through normal cell signalling processes, may stimulate osteoclasts to effect a degree of bone

Please cite this article in press as: David F. Williams, On the mechanisms of biocompatibility, Biomaterials (2008), doi:10.1016/j.biomaterials.2008.04.023

resorption, leading to loosening of the prosthesis [13]. The chemistry of the polymer is not relevant to the inflammatory process, and indeed osteolysis and prosthesis loosening have been observed with polymers other than polyethylene [14], and the only factors are the rate of wear debris release [15] and the physical form and dimensions of the particles [16]. Although there have been many attempts to improve the polyethylene, none have been clinically relevant other than those which reduce the wear rate, principally through cross-linking and control of sterilisation procedures [17]. It is possible that the host response can be marginally modulated pharmacologically, through the use of bisphosphonates or vitamins for example [18], most likely to be given systemically.

Ceramics are involved in joint replacements in two different circumstances. Inert oxide ceramics may be used as bearing surfaces, where their hardness improves wear resistance and therefore minimises osteolysis, with an increasing use of alumina–alumina combinations [19]. There are no other biocompatibility considerations with ceramic bearing surfaces other than minimising degradation or wear. On the other hand, bioactive ceramics and glasses, principally hydroxyapatite, various calcium phosphates and bioactive glasses, are used as coatings to improve bone bonding [20–22]. More will be said in a later section about the use of such materials in tissue engineering and drug delivery situations, but their role in long-term implantable devices is rather restricted. There is evidence of some clinical utility as coatings on uncemented joint prostheses, especially with respect to the kinetics of bone adaptation, where the performance is based on the balance between the facilitation of bone formation and the resorption or stability of the materials [23,24].

As a result of this analysis based upon clinical experience and recent experimental studies, the only materials significantly used in joint prostheses are titanium and cobalt–chromium alloys, cross-linked UHMWHD polyethylene, alumina, PMMA for cement and hydroxyapatite for a bioactive coating. The only criteria for biocompatibility are the need to minimise the release of any degradation or wear particles or corrosion products, and to maximise the rate and efficiency of bone adaptation. With the possible exception of improving bone bonding through bioactivity, where the magnitude of the effect is probably only marginal, there is no benefit from seeking characteristics of the materials other than they are as inert as possible. There are many examples of attempts to increase performance through materials ‘improvements’ but virtually all have actually led to a diminution of performance, including porous metal backed acetabular components [25], alternative polymers to polyethylene [26], alternatives to alumina such as transformation toughened zirconia [27] for bearing surfaces, and alternative forms of acrylic cements [28]. Provided the choice of materials is confined to this very narrow range, the materials themselves play very little role in determining the outcome of the procedures, where the most important determinants of performance are surgical and nursing skills, patient compliance and infection control [29].

4.2. Intraocular lenses and other ophthalmological devices

Within the eye there are several devices with a reasonably long record of use, including intraocular lenses and artificial corneas, or keratoprostheses, where functionality is largely determined by the optical properties, the physical compatibility with the relevant tissue and the insertion into and retention within the desired location. Biocompatibility is determined by the need to minimise the extent of the tissue reaction in order to avoid compromising the light transmission. Intraocular lenses are remarkably successful implantable devices, primarily used in patients with cataracts following removal of the affected lens [30]. Two broad classes of material have been used, silicones and acrylics, although the descriptive literature on these materials is usually very general and each term covers a multitude of specific types. At this time there is little to choose between these with respect to the biocompatibility, although clinical performance will vary as a function of factors of design, clinical technique and patient variables [31]. Both types of material are very resistant to degradation and leachables are effectively absent. Variations within each class are normally concerned with either chemical structure or surface modifications that control either or both the hydrophobic/hydrophilic nature and the flexibility, mostly in relation to the clinical techniques and implant functionality. The cataract literature rarely discusses biocompatibility issues in conventional designs and patients, but is far more concerned with extending the technique, for example towards accommodating and multifocal lenses and blue light absorbing lenses to protect against age-related macular degeneration, and to the use in more difficult patient groups, including paediatric cases, diabetics and those with other eye conditions [32]. Although, in theory, the surface characteristics of the lenses should affect the local tissue response, including protein adsorption, epithelial cell overgrowth, inflammation and so on, in the vast majority of situations this is of no clinical relevance. At one time it was considered important to control inflammation by surface modifying with heparin, for example, but no significant improvements are now found and in fact the heparin modified surfaces may be associated with greater levels of posterior capsule opacification [33]. It may well be that in certain patients with either localised (e.g. uveitis) or systemic (diabetic) conditions, some lens material features will be relevant, for example the flexibility which determines the size of the incision through which the lens is inserted, but this is not generally the case. Indeed it seems likely that the performance of intraocular lenses has very little to do with the precise nature of the material and much more to do with clinical technique, including inflammation and infection control, and the general state of health of the patient. Although far less advanced, the area of corneal replacement is somewhat similar, where biostable transparent polymers, including hydrogels such as poly(hydroxyethylmethacrylate), appear to give good performance, in this case the main challenges being concerned with prosthesis anchorage [34].

4.3. Devices for cardiac rhythm management

Cardiac pacemakers and implantable cardioverter defibrillators (ICDs) provide an exceptionally successful technology platform for the management of a wide variety of cardiac rhythm disorders. They are complex implantable devices, but performance is largely independent of the nature of the biomaterials used in their construction now that basic lessons have been learnt. Almost universally, the active components are encapsulated in a hermetically sealed titanium can, whose biocompatibility characteristics are controlled by the corrosion resistance of this metal. Leads transmit pulses for both sensing and delivery purposes from the can to the electrode placed at the relevant site on the heart. The functional properties specified for these components are clearly related to the electrical performance and most systems use one of a small number of high electrical conductivity, fatigue resistant and corrosion resistant alloys such as those of the platinum group metal alloys or the cobalt–chromium group such as Elgiloy for the leads and electrodes [35], with an insulating sleeve covering the lead [36]. Well known problems with the cracking of polyurethane insulating leads, including stress cracking and metal ion-induced oxidation [37], have largely been solved and polyurethane and silicones are now standard. As far as the electrode is concerned, the main requirement is concerned with the delivery of the electrical impulse without the inducement of excessive fibrosis, which could raise the threshold stimulus to clinically unacceptable levels. This is an important biocompatibility issue, since the function of the electrode is to deliver impulses that involve the transfer of ions across the

Please cite this article in press as: David F. Williams, On the mechanisms of biocompatibility, Biomaterials (2008), doi:10.1016/j.biomaterials.2008.04.023

interface and, by definition, this function must be capable of influencing the tissue response. There is no clear resolution to this, with parallel attempts to minimise the ion transfer through coatings such as iridium oxide [38] or titanium nitride [39] and to minimise the host response through the delivery of an anti-inflammatory agent to the tissue [40]. The situation is, therefore, that inertness is a principle specification for the biomaterials used in these implantable electronic devices, with the caveat that the functional characteristics of the leads, insulators and electrodes may impact on the host response and it may be beneficial to intervene in this response in order to optimise the clinical outcomes. The vast majority of pacemakers do not employ either mechanism and it may well be that the ICDs, which are of more recent origin and now increasing in popularity, would benefit more [41]. It is also noticeable that these rhythm control devices are being used in more cases in children and there appear to be more persuasive arguments that this intervention in biocompatibility should be considered in these paediatric cases [42].

4.4. Soft tissue reconstruction and augmentation

The use of implantable devices in soft tissue replacement and augmentation has a long and varied history, and this has generated a series of biocompatibility controversies. The story of breast implants is far too long and complex to discuss in any detail here, but the lessons are profound. A brief summary of the issues is as follows. Implants are used for the replacement of breast tissue following mastectomy or for the augmentation, or enlargement or re-shaping of the female breast. The functional requirements are that the materials and device designs should allow the replication of the physical characteristics of breast tissue, which is composed of fatty and glandular tissue, with long-term maintenance of shape and volume. This is not a trivial specification since no homogeneous solid synthetic material has these characteristics. The vast majority of breast implants follow the concept of using an elastomeric shell that contains a gel, the latter to give the required consistency and the former to encapsulate the gel and give size and shape. For many years, the optimal functional performance was provided by a combination of a silicone gel and a silicone elastomer shell [43].

The first problem to arise with these silicone breast implant was the development, in a significant number of patients, of an excessively thick fibrous capsule, the so-called constrictive fibrosis or capsular contraction, which was highly clinically significant in many patients because of the distortion and pain associated with the contraction. In spite of many attempts to do so, there has been no correlation between the fibrosis and any chemical or toxicological feature of the silicone materials, or the silica filler that is present in the elastomer [44]. On the other hand, there is good evidence to suggest that this fibrosis is due to mechanical irritation and cellular stimulation associated with the micro-movement of the implant–tissue interface, bearing in mind that these devices are amongst the largest of all implants, and breast tissue is naturally subjected to significant movement.

The desire to produce implants with more natural consistency led to devices with much thinner elastomer shells and, without any doubt, these did experience a finite incidence of mechanical failure, the so-called implant rupture. In spite of claims to the contrary, this has not been the result of ageing or degradation of the silicone elastomer, which would be a significant and important biocompatibility factor, but is purely mechanical [45]. On the other hand, there is no doubt that some silicone components could diffuse through the silicone elastomer shell, the so-called gel bleed, and there have been significant questions about how much diffusion takes place, where the diffusing molecules go and what are the consequences. The controversy has generated criticisms of silicones, which have involved claims of widespread release and distribution of various silicone components, including oligomers, fillers and catalysts, and a resulting cascade of clinical consequences including the development of autoimmune conditions [46], including scleroderma, lupus and rheumatoid arthritis, peripheral neuropathy [47] and a wide variety of degenerative diseases, and also self-reported conditions without specific diagnosis [48]. There can be no doubt that the vast majority of claims about the detrimental affects of silicone entities have proven unfounded, following both epidemiological, clinical and experimental studies [49]. Although there are still some studies showing a strong T-cell immune response associated with the surrounding tissue in some patients [50], the widespread claims of major immune responses to these implants have been discredited and there are no significant lessons for biocompatibility from these cases. Indeed, the converse may well be true since the precautionary regulatory disapproval of silicone breast implants prompted some attempts to use alternative fillers for implants, including cellulosic [51] and lipid derivatives [52] where limited clinical studies confirmed the rather delicate nature of the breast implant scenario. The use of a soya-bean lipid gel within a silicone elastomer has in fact revealed a sequence of biocompatibility disasters, including the potential mutagenic properties of the molecules resulting from the peroxidation of the lipid, and the degradation of the silicone produced by prolonged contact with the lipid [53].

4.5. Heart valves

The replacement of diseased heart valves has been possible for well over 40 years. Taking first the mechanical heart valves, the materials have changed very little in this time, and neither has the rationale for their selection. The vast majority of valves used during this time have had an annulus/frame made of an alloy, usually titanium alloy or cobalt–chromium, the annulus being covered by a fabric sewing ring, almost exclusively of either expanded PTFE or polyethylene terephthalate textile, with an occluder or leaflets made of a carbon substrate with a pyrolytic carbon surface. The alloys have been chosen to minimise corrosion whilst maintaining adequate mechanical properties. A few well known valve failures have been attributed to issues with the mechanical properties of these alloy components, including fatigue [54], but none to corrosion and metal ion release problems. The choice of sewing ring material has largely been based on the ease of suturing to the cardiac muscle coupled with minimal degradation and minimal interference with the healing response and there has been no perceived benefit from deviating from this choice. The selection of pyrolytic carbon for the critical occluder component is based on the need to minimise the tendency to initiate blood clots, coupled with mechanical robustness. This is an immensely important aspect since the inherent haemodynamic characteristics of a mechanical valve imply that blood clots are very likely but it is extremely improbable that any different materials would make this situation any better. With all mechanical valves, this issue is addressed by systemic anti-coagulation [55]. Exactly as with joint replacement prostheses, provided the choice of materials is confined to a very narrow range, the materials themselves play very little role in determining the outcome of the heart valve replacement, where the most important determinants of performance are surgical and nursing skills, patient compliance with their anti-coagulation, other concurrent cardiovascular disease, and infection control. With the latter situation, endocarditis, which probably affects 1% of patients is often fatal, and is preferably controlled by prophylactic systemic antibiotics [56]. The one situation in which localised antibacterial activity was attempted, using silver, did not prove clinically effective [57].

The possibility of thromboembolic events arising from mechanical valves has led to an increasing use of bioprosthetic valves

Please cite this article in press as: David F. Williams, On the mechanisms of biocompatibility, Biomaterials (2008), doi:10.1016/j.biomaterials.2008.04.023

over the last 20 years. These have, in general, fallen into three groups, the porcine xenograft, the bovine pericardial valve, and the human aortic valve allograft, also known as a homograft. The homograft has very good performance but with problems of limited supply and the possibility of transmission of bovine spongiform encephalopathy has essentially eliminated bovine derived bioprostheses, so we may confine our comments to the porcine xenografts. These valves, being of natural design and construction, give good haemodynamic performance. As far as their biocompatibility is concerned they do have an advantage over the mechanical valves since they are not intrinsically thrombogenic and do not necessitate anti-coagulation therapy. They do, however, offer two challenges, based on the susceptibility of the collagen, upon which they are largely based, to denature and degrade, and to calcify, and also possibly stimulate an immunological response or transmit infection [58]. The early, and indeed still the most popular, type of porcine bioprosthesis has addressed all of these issues through one simple procedure, that of a chemical pre-treatment with the cross-linking agent glutaraldehyde which simultaneously minimises infection risk, reduces the immunogenicity and enhances resistance to enzymatic and chemical degradation of the collagen [59]. However, several concerns arise from this process, the first being that the glutaraldehyde, and several of its derivatives, are both leachable and cytotoxic, and a great deal of effort has been spent in attempts to develop less cytotoxic and more effective cross-linking agents. This is a clear example where methods designed to counter one biocompatibility deficiency often introduce other deficiencies. The second is that the already noted susceptibility to calcification is potentially enhanced by the glutaraldehyde procedure, the mechanisms of which have been discussed many times and still not fully elucidated [60]. It is now being increasingly accepted that insufficiently masked immune responses and related inflammation significantly affect susceptibility to calcification and degradation [61]. The result is that calcification is considered an inevitability with porcine xenografts and although there are variations in the process, for example through the use of an ethanol pre-treatment and other anti-calcification agents, and indeed variations in the susceptibility of patients, it is generally agreed that 20 years is a maximum that should be expected.

This has led to some profound re-evaluation of the use of so-called natural tissues as materials for long-term implantation, especially in the context of biocompatibility and the rationale for regeneration instead of replacement. The need for better performance from the bioprosthetic valves has led to the introduction of alternative tissue treatments, and especially those that are aimed at specifically removing all of the cellular remnants that are considered to promote calcification and immune responses, usually through processes of osmotic or enzymatic de-cellularisation [62]. Although the results may be variable, with some groups reporting success, it is widely recognised that this process can have devastating consequences. It was originally postulated that the decellularised tissue would become repopulated with host valvular cells [63]. This, however, does not necessarily occur, as shown with a series of fatalities in paediatric cases with congenital valvular malformations in which there were severe foreign body reactions, involving neutrophils and macrophages and, later, lymphocytes. There was no repopulation with the required fibroblasts and myofibroblasts but instead the formation of fibrous hyperplasia with calcific deposits, which led to both stenosis and rupture/disintegration [64]. The biocompatibility implications here are clearly that the collagenous structure of the porcine aortic valve material is reactive with and responsive to the human physiological environment and must ultimately fail because of the ensuing interactions, most notably leading to loss of structural integrity and calcification. Attempts to ameliorate the long-term problems have led to greater variability but generally with even less control of the immune and inflammatory responses, calcification and structural deterioration. The situation is obviously different to that with mechanical valves, but the underlying principles with respect to biocompatibility are just the same. If it were not for the advantage with respect to haemocompatibility, it is unlikely that the biocompatibility of xenograft valves would be considered sufficiently good to justify their use.

4.6. Intravascular stents

The situation with intravascular stents represents a powerful reminder of the fragility of the material–tissue interface. Balloon angioplasty, introduced a couple of decades ago, was a remarkably successful addition to the methods available for the treatment of atherosclerotic occlusion of arteries, especially of the coronary arteries [65]. However, the mechanical interference with the endothelium during this procedure led, in many patients, to the recurrence of the stenosis as the endothelium and smooth muscle cells reacted to this transient injury. The answer to this dilemma was the intravascular stent, in which an expandable tubular stent was deployed within the lumen of the vessel, thereby physically holding the vessel open [66]. Because of the need for the appropriate mechanical characteristics compatible with stent deployment, the stents have typically been made of stainless steel [67], a shape memory nickel–titanium alloy (such as Nitinol) [68], or a cobalt–chromium alloy [69]. These bare-metal stents have served well, but not well enough in most cases, as in-stent re-stenosis often eventually appeared [70]. The evidence would suggest that choosing alloys that were as corrosion resistant as possible has been insufficient here to guarantee the desirable level of biocompatibility, since the irritation to the adjacent tissues has been physically rather than chemically induced, but this does not negate the general principles of materials' selection noted before.

Two additional features of stents add to the complexity, but paradoxically underline these principles. The first concerns the use of drug eluting stents, where, typically, the metal stent is coated with a thin layer of polymer which incorporates an appropriate drug, the release of which causes the down-regulation of the cell proliferation processes that cause the re-stenosis. Not surprisingly, this procedure has not been without controversy for, although the clinical trials published thus far indicate a marked improvement in the patency of stents over time, there have been issues over the raised levels of thrombosis, both in the early stages post-operative [71] and later, potentially equating with the time point when all of the available drug has been eluted or related to the post-operative pharmacological regime [72]. The second feature concerns the desire to eliminate the biocompatibility problems of stents by making them biodegradable. There have been some attempts to use biodegradable polymers [73] and also a small group of so-called bioresorbable magnesium alloys [74]. The latter stents can be designed to corrode over a time scale ranging from a few weeks to months. Again not surprisingly here the evidence is equivocal since there is undoubtedly a greater tissue response to the corroding metal, leading to initial inflammation and hyperplasia, but then with claims that the endothelium remodels once the metal has been resorbed. Magnesium is a good choice in the sense that its toxicity is minimal, but the degradation process inevitably leads to the release of particulate products, which are intrinsically irritant and pro-inflammatory. A recent review summarises the uses of biomaterials in stents very well [75].

4.7. Vascular grafts

Vascular grafts have been in clinical use for well over four decades. The current position is that although synthetic grafts, usually made from an expanded polytetrafluoroethylene or a polyethylene

Please cite this article in press as: David F. Williams, On the mechanisms of biocompatibility, Biomaterials (2008), doi:10.1016/j.biomaterials.2008.04.023

terephthalate based textile, are available, there is a limitation on the situations in which they may be used, and autologous vein grafts, such as the saphenous vein, are either mandated, such as in coronary artery bypass, or often preferred, as in femoro-popliteal bypass. The reasons for this situation are based on the ability of such grafts to remain patent, with appropriate haemodynamic performance, for a clinically acceptable time. This is clearly related to the fundamental biocompatibility characteristics of the graft, although the specific effect of the graft material per se on this biocompatibility is far from obvious. The two principal material structures mentioned above appear to behave in a similar manner [76]. Soon after implantation there will be thrombus formation within the pores of the graft and the initiation of an exudative inflammatory response, with a cellular infiltration, of local origin, on the outer surface of the prosthesis, and of haematogenous origin on the luminal aspect. This is followed by a reparative–proliferative phase involving fibroblasts, with connective tissue, primarily collagen, forming within the vessel wall. There is also a continued maintenance of a macrophage/foreign body giant cell response. Usually there is an increasing proliferation of an inner mesenchymal lining to the vessel without any significant endothelialisation and it is this so-called intimal hyperplasia that is the cause of the loss of patency eventually seen with these devices. The region of hyperplasia is composed of around 20% vascular smooth muscle cells that migrate through the vessel wall and which deposit an extracellular matrix, and a number of inflammatory cells, including macrophages and lymphocytes [77].

In the majority of situations, the clinical outcomes with respect to synthetic vascular grafts are inferior to those obtained with vein grafts. A recent systematic review of reports on clinical data concerning above-knee femoro-popliteal bypass [78] concluded the five year patency rate for saphenous vein grafts was 74% but only 39% for ePTFE bypass grafts. This clearly indicates that the biocompatibility of the synthetic grafts is less than optimal. The question arises as to whether there is any difference in the performance of different types of synthetic graft. For some years it was generally thought that ePTFE gave better patency rates, but this is not necessarily so. One recent study [79] concluded that long-term outcomes with Dacron and ePTFE for femorofemoral bypass were equivalent and that the preferential use of ePTFE in this situation was not justified. A further review [80] showed that in femoropopliteal bypass, secondary patency for saphenous vein grafts was 90% whilst for ePTFE it was 47% and for Dacron 60%.

In terms of mechanisms by which biomaterials may influence this hyperplastic response, two factors may be considered relevant, related to their effects on thrombosis and inflammation, although these two processes are linked. The complexity of biomaterial-associated thrombosis has recently been reviewed by Gorbet and Sefton [81] who persuasively argue that activation of contact phase proteins (as implied in the intrinsic pathway of blood coagulation) is unlikely to be important in the activation of coagulation by biomaterials, including those used in vascular grafts. Instead, they argue that the extrinsic pathway, involving tissue factor expression by a variety of cells following vascular damage, such as neutrophils and monocytes, is important. Indeed, it may well be that it is material-induced leukocyte activation that is the principal mechanism involved in the thrombosis that occurs within a vascular graft. Thus, all of the concepts about the control of thrombogenicity through the physico-chemical characteristics of the biomaterial surfaces and their interaction with plasma proteins and platelets may have little or no relevance to vascular grafts; instead it is the control of the interactions with leukocytes, and their mediation of inflammation in general, that is important. The marked difference between the critical surface tension of PTFE (19 dynes/cm) and polyethylene terephthalate (43 dynes/cm) makes little difference to their performance in vascular grafts. Salzmann et al. [82] have drawn attention to the ability of vascular grafts to stimulate chronic inflammation and shown an inverse relationship between this ability and neovascularisation within the grafts, speculating that this is an important factor in intimal hyperplasia; certainly the presence of macrophages in the connective tissue within the graft wall can be expected to stimulate hyperplasia through their release of proliferation-enhancing cytokines. Although there were differences between different types of commercial graft, these were not uniformly correlated with the graft material, but more related to the microarchitecture of the grafts. These views on the importance of inflammation compared to thrombosis are consistent with the indications that inflammation is the key driver of re-stenosis after angioplasty in patients with peripheral artery disease, the biochemical markers of coagulation showing no correlation with stenosis [83].

Polytetrafluoroethylene and polyethylene terephthalate are not normally used in other equivalent implantable situations and it is difficult to compare their general performances, but, should the outcomes with respect to vascular grafts be dependent on their pro-inflammatory nature, it is not surprising that these should be essentially similar, at least during the short and medium term. There is no reason to believe that these materials would intrinsically exert different stimuli to inflammation and hyperplasia in the vascular graft situation during the normal time scale of clinical performance. It is interesting to note that polyethylene terephthalate is ultimately biodegradable, through either hydrolysis or enzymatic attack, as shown many years ago by the present author [84], consistent with increasing case reports of Dacron graft degradation and breakdown, often after 15 or more years (for example see Refs. [85,86]). It is also relevant that no other material has been successfully introduced into vascular grafts during the last several decades. There has been much discussion about the potential for polyurethanes [87] but their inherent susceptibility to biodegradation has been a limitation. It has to be said that a degradable vascular prosthesis is not out of the question and several experimental studies, for example those of Greisler [88], indicate that tissue regeneration may take place within a degrading prosthesis.

It should be noted that there has been some apparent success recently with the coating of vascular grafts by heparin, Heyligers et al. [89] showing in vitro evidence of both anti-coagulant and anti-platelet effects with heparin-bonded ePTFE, Devine et al. [90] showing a short term beneficial effect of heparin-bonded Dacron and both Walluscheck [91] and Peeters et al. [92] recording medium term improvements of ePTFE by heparin coating in various anatomical sites. Since heparin has both anti-coagulation and anti-inflammatory effects, this evidence cannot distinguish mechanisms. However, it is of relevance that another approach to modulate the processes of intimal hyperplasia involves the molecule nitric oxide, which normally provides an effective endogenous resistance to leukocyte adhesion and activation, platelet aggregation and the proliferation of vascular smooth muscle, and which is itself inhibited by the products of vascular tissue injury. There is now some evidence that a nitric oxide producing or releasing surface could reduce intimal hyperplasia [93] suggesting that the sustained inhibition of inflammation, by either heparin or nitric oxide could be very beneficial.

It is a widely held view that synthetic vascular grafts work reasonably well in high flow situations, but far less well under low flow. As reviewed recently by Cunningham and Gotlieb [94] the pathobiology of atherosclerosis and the related therapy related phenomena of re-stenosis and hyperplasia, is largely dependent on blood flow induced shear stresses. In vascular grafts these stresses are themselves related to the design and mechanical compliance of the graft, providing further reasons why, in the majority of circumstances, provided the material is minimally pro-inflammatory, it actually has very limited influence on the tissue response within

Please cite this article in press as: David F. Williams, On the mechanisms of biocompatibility, Biomaterials (2008), doi:10.1016/j.biomaterials.2008.04.023

and around the graft. It is also relevant that in untreated blood vessels the maintenance of laminar flow and physiologic shear stresses is a pre-requisite for normal vascular function and that the introduction of flow disturbances is the cause of abnormal behaviour [95], including changes to endothelial cell gene expression, the initiation of oxidative and inflammatory states in the endothelium and leukocyte adhesion. In vascular grafts, it is usually the sites of anastomoses that cause the most significant flow disturbances and altered shear stress patterns, and it is here that the intimal hyperplasia is mostly found.

The clinical performance of vascular grafts would undoubtedly be much different if they were able to form a uniform endothelial lining, but this rarely happens unaided in humans. There have been many attempts over 20 or so years to solve this problem by seeding the grafts prior to implantation with autologous endothelial cells. The fact that this can be achieved and used for routine clinical procedures to give significantly improved patency rates has been demonstrated by Zilla and colleagues [96].

In an attempt to rationalise why prosthetic vascular grafts do not give better clinical performance [97], Zilla has analysed the experience over the last half century and determined that one of the major reasons lies with the fact that the majority of grafts are so impervious that transmural tissue ingrowth is impossible, such that none develop a neointima except for sporadically observed small islands of endothelium. Moreover, the build-up of the hostile biological environment in the inner layers of prosthetic grafts inhibits capillary ingrowth. Even though the temporal pattern of cellular events around the graft is obviously important, for example involving the role of macrophages in the secretion of cytokines, the precise functioning of the graft materials with respect to the influence of their intrinsic biocompatibility has not been resolved. However, there is little or no evidence that deviating from chemical inertness is of any value; it is no accident that the best patency rates are achieved with the most chemically inert polymers.

5. Degradable implantable systems

One of the first reasons for modifying the concept of biocompatibility arose with the development of degradable implantable materials and systems, where a stable equilibrium was emphatically not desired, but where the degrading material had to perform a function before or during a process by which it was degraded and eliminated from the body. Initially the focus was on absorbable sutures where, for many years, surgical catgut had been the only clinically acceptable material but, being derived from animal sources, did suffer from relatively poor reproducibility and an aggressive tissue response. A series of poly(lactic acid) and poly(glycolic acid) based materials, and later some other aliphatic polyesters was introduced which generally appeared to display superior biocompatibility, implying a greater reliability in degradation rates and acceptable host responses to the degradation process. Although such materials can be affected by tissue enzymes and other active chemical species such as superoxides and free radicals [98], it is generally agreed that the degradation occurs through hydrolysis, the ultimate degradation products being water soluble monomer, dimers or oligomers of the respective acid [99]. The host response to these sutures and similar devices has involved the presence of inflammatory cells over the course of the degradation period but with no clinically unacceptable outcomes. The biodegradable polyester suture material has become the model for clinically acceptable biocompatibility performance with intentionally degradable implant systems, bearing in mind the relatively small volume of material used, the 3–12 weeks' degradation profile and the apparently physiologically acceptable products of degradation and resorption. The question arises as to if, how and where degradable systems do not show acceptable biocompatibility.

Of some significance here are the observations that have been made of clinically inappropriate responses with some larger devices made of the same polyesters used in fracture fixation. As reviewed by Bostman and Pihlajamaki [100], a series of clinical studies were reported in the early 1990s where there were significant inflammatory reactions to polyester orthopaedic and maxillofacial implants, usually occurring during the late phase of degradation, sometimes many years after implantation [101]. There are several possible causes of this phenomenon, with the release of a large volume of pro-inflammatory crystals of micron size towards the end of the process, the low pH that may be associated with these last stages, and the potential release of residual catalysts all being invoked at various points, but the essential feature is that either the physical presence of particulate degradation products or the transient chemical characteristics of the degrading milieu are able to stimulate inflammatory cells, especially macrophages and giant cells, at any such time as their presence exceeds a certain threshold. There have been some suggestions that this is dependent on the nature of the polyester used, for example with claims that it occurs more frequently with polyglycolides than polylactides [102] but this is unlikely to be a simple matter of implant chemistry rather than the characteristics of the degradation profile. This profile may be indirectly related to morphological features such as the crystallinity. Interestingly Chen and colleagues [103] in various studies on the polyhydroxyalkenoate (PHA) family of polymers have reported far less of an inflammatory response with poly(3-hydroxybutyrate-*co*-3-hydroxyhexanoate) systems than with polylactides, attributing this to a slower degradation rate and less acidic and apparently less inflammatory products of degradation. Significantly, blending the polymer with polyethylene glycol significantly accelerated degradation and concomitantly increased the inflammatory response.

Many degradable polymers have been incorporated into drug delivery systems, often as microspheres and more recently as nanoscale entities. Anderson has discussed the phenomena of biodegradation and biocompatibility with the former systems on several occasions, for example with respect to polylactide and polyglycolides' microspheres [104], and it seems very clear that, with materials such as these, the tissue response follows a straightforward pattern. Immediately after the parenteral injection of microcapsules, there will be acute, sub-acute and chronic inflammatory responses, largely mediated by the mechanical injury of injection and the physical presence of the particles, monocytes soon becoming the dominant cell. For the duration of the presence of the microcapsules, and to some extent depending on their size and size distribution, there will be a macrophage/giant cell/fibroblast response, which will then be resolved once the microspheres fragment and disappear, often involving phagocytosis by the macrophages and giant cells. Whether or not there will be a residual fibrous capsule depends on the intensity of this process, the kinetics of degradation and the site of injection.

The response to microspheres is not always so straightforward. Fournier et al. [105] have reported the results of the response of rat brain to biodegradable poly(methylidene malonate) microspheres. Their work follows on from the characterisation of the degradation profile of this polymer by Le Visage et al. [106] who showed that one pathway of degradation was by hydrolysis of side chain ester groups leading to the release of glycolic acid and ethanol and leaving a residual polycarboxylic acid, which would be gradually solubilised. Fournier et al. [105] revealed two pathways, with direct hydrolytic scission of the polymer chain, leading to the release of formaldehyde and an alkyl cyanoacrylate in addition to the side group hydrolysis. They found that microspheres of the polymer, when implanted into the brain, elicited only a mild initial inflammatory reaction, which became essentially quiescent until the microspheres began to visibly degrade at about six months, when

Please cite this article in press as: David F. Williams, On the mechanisms of biocompatibility, Biomaterials (2008), doi:10.1016/j.biomaterials.2008.04.023

a significant inflammatory reaction was reactivated, with a clear direct toxicological effect on the surrounding tissue as the degrading polymer formed a gel. It was argued that the acidic nature of the solubilising residual polymer had a direct cytotoxic effect, producing what was described as irreversible tissue destruction, although it cannot be ruled out that the cyanoacrylate and formaldehyde were not themselves involved. A similar biocompatibility problem has arisen with a degradable orthopaedic adhesive intended to augment the use of fracture screws. Alkylene bis(dilactoyl) methacrylate was developed for this purpose, synthesised from ethylene glycol, lactic acid and methacrylic acid and although initial studies showed reasonable responses, two detailed longer term studies in large animal models showed massive local inflammatory responses and osteolysis as the polymer degraded [106–108]. Degradation mechanisms are not clear but the similarities are striking and the inflammation would appear to be associated with a combination of the physical presence of fragmenting polymer and the residence in the local tissue of solubilising molecular residues of the degradation process. Obviously these considerations need to be borne in mind with the development of other degradable polymer systems, such as some polyurethanes [108], where the profile of side group and main chain hydrolysis and the solubilisation and distribution of the resulting molecules have to be taken into account.

It should be noted here that significant interest has been shown to entities of very small dimensions in the development of more precise and efficient delivery systems, especially for complex pharmaceutical and gene delivery processes. At one stage microspheres were very popular but in the last five years it is the nanoscale that has received most attention. By definition [109] the nanoscale means of the order of 100 nanometres or less, and a wide range of nanoparticle based formulations have been developed and assessed. The understanding of the biocompatibility of nanoparticles is in its infancy, and factors such as the ease of translocation of nanoparticles throughout the body, possibly including the brain, and across membranes, including cellular membranes and the blood–brain barrier, and their ability to directly interact with DNA are obviously important [110–112].

6. Transient invasive intravascular devices

Large numbers of patients, such as those undergoing haemodialysis, come into contact with biomaterials through the insertion of a catheter into their venous system, either for a short term delivery of some substance for nutritional, diagnostic or therapeutic purposes, or for more long-term purposes. The intervention may be either central or peripheral. For many years it has been recognised that these interventions are not without risk, largely related to either infection or thrombosis and their sequelae. Because of the well known propensity for foreign materials to induce thrombosis, it might be assumed that the inherent blood compatibility of the catheter materials was of critical importance in the selection of suitable materials. Some 25 years ago, the materials selected included various forms of polyethylene, PVC, PTFE, silicone elastomers and polyurethanes. A few studies were performed (for example see Ref. [113]) which attempted to compare different materials but these were never of real value in determining mechanistically how materials performed, although through rarely documented procedures, the first three of these materials were largely discarded such that today it is mainly the silicones and polyurethanes that are used [114]. A comprehensive review of risk factors for deep vein thrombosis related to central venous catheters [115] has considered patient characteristics and the catheter itself and there can be no doubt that the former (including inherited coagulation disorders and the disease state, such as cancer) are likely to be as significant as the catheter features. Within the latter category, the number of lumen in the catheter, the puncture site and the eventual site of the catheter tip appear to be more important than the precise material. The situation is, therefore, that there is little, if anything, to choose between silicones and polyurethanes for these applications and nor is there any substantive data to explain why these give better clinical performance than other polymers. It is in fact likely that non-blood compatibility factors are involved, since the flexibility of the catheters and the lubricity of their surfaces are of utmost importance from a clinical handling perspective and almost certainly silicones and polyurethanes will be superior to all the other materials mentioned in relation to these properties.

It cannot be claimed that these two families of polymers represent optimal biocompatibility in the context of venous catheters, but it is far from clear how material, or material-surface specific effects are involved with any thrombolic event. Many catheters do eventually become enveloped in a fibrin sheath, but this has not mechanistically been related to any material property nor to any relationship between a material surface and any of the protein adsorption phenomena that are thought to take place at the interface. As discussed by Brash [116] there are several such phenomena that are potentially involved in the processes of blood–material interactions, and indeed can be demonstrated experimentally, and which lead to theoretical methods of minimising these interactions, but there is little evidence yet to show how any of these can be of help in the complexity of the clinical application. Systemic heparin is known to be of help in some situations and this fact has now been translated to the use of heparin-coated catheter materials, notably polyurethanes, at least in the short term [117]. The performance may be improved by using covalent complexes of heparin with antithrombin [118].

7. Tissue engineering scaffolds

7.1. Background

Notwithstanding the routine clinical successes with many of the long-term implantable devices discussed in Section 4 above, there are significant limitations to the approach of using manufactured prosthetic devices for the treatment of chronic diseases or injuries. Biocompatibility considerations obviously provide one category of limiting factors although we have seen that, provided certain basic rules are followed, these do not constitute difficult barriers in most situations. As discussed by the author elsewhere [119], the major limitations are based on the fact that non-viable replacements for tissues and organs can largely address only their physical and mechanical deficiencies on a long-term basis and there is simply no options for the use of synthetic structures to replace the biological (e.g. metabolic) functions. A fundamental shift in the approach to therapies for many diseases has been witnessed during the last decade, through the various strategies within the broad area of regenerative medicine. Usually taken to include cell therapies, gene therapy and tissue engineering, these are essentially aimed at regenerating diseased tissue rather than replacing it with synthetic materials. Tissue engineering has been defined conceptually as [2]:

> *'The persuasion of the body to heal itself, through the delivery to the appropriate sites of molecular signals, cells and/or supporting structures',*

but is perhaps better seen at a more practical level as:

> *'Tissue engineering is 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'*

It will be seen that tissue engineering is concerned with the stimulation of cells, from wherever they are derived, to generate

Please cite this article in press as: David F. Williams, On the mechanisms of biocompatibility, Biomaterials (2008), doi:10.1016/j.biomaterials.2008.04.023

new tissue, often through the expression of extracellular matrix, for the functional restoration of tissues or organs. This is not a trivial task since most of the affected cells in human adults do not innately have this capacity, hence the emphasis on controlled and systematic stimulation. Although the use of a biomaterial is not mandatory in tissue engineering (which itself calls into question the boundary between tissue engineering and cell therapy), most attempts to accomplish this stimulation have involved biomaterials in one form or another, partly to impart shape to the tissue that is being regenerated, and partly to facilitate the stimulation via molecular and/or mechanical signals.

Tissue engineering may be achieved through several different routes but there is a basic paradigm of ex vivo tissue regeneration, discussed recently [120] which may serve as a template, in which there is a progression from cell sourcing through cell manipulation and signalling to tissue expression and construct formation, followed by implantation into the host and its full incorporation into that host. In the centre of this paradigm is the seeding of the required cells into a biomaterial scaffold or matrix, wherein they produce the new tissue. Usually, although not necessarily, the biomaterial is required to degrade or dissolve as the new tissue forms.

Obviously the biocompatibility of the biomaterial is crucial in this process and here we see a distinct departure from the desirable characteristics of biocompatibility discussed in relation to almost all previous biomaterial scenarios. Whereas with implantable devices, drug delivery systems and intravascular invasive devices, the key to biocompatibility success with any material has been to achieve a physical or mechanical function without eliciting any unusual response from the relevant tissue, with a tissue engineering scaffold or matrix, the whole point is that the material should be designed to actually elicit such a response. It is poignant and relevant to note that the vast majority of attempts to produce scaffold-based tissue engineering products have been predicated on the perceived requirement that the material should have had previous regulatory approval within the context of medical devices, a specification which may have a practical (and economic) basis, but which is fundamentally in error from a scientific point of view. The question today is that if such a specification is erroneous, what are better specifications for tissue engineering biomaterials with respect to biocompatibility?

7.2. The essential material specifications for a tissue engineering scaffold

Let us assume for a moment that, within the basic paradigm outlined above, we wish to use a biomaterial to support cells in an ex vivo culture system. Let us further initially assume that the material is to be used as an open porous system and that the cells are fully differentiated cells derived from a biopsy taken from the eventual host. The question naturally arises as to the nature of the specifications of the optimal materials for those scaffolds. The apparently successful use of degradable polymers in medical devices has, unfortunately, been extrapolated into the 'potential' for such materials to be used in tissue engineering products, without an understanding of the requirements and specifications for these two quite different applications. There is a large difference between the requirements of a biodegradable material for a medical device, which as we have seen should not interfere at all with any biological process, and a biodegradable scaffold material, which should assist in the biological processes associated with regeneration.

The current situation with respect to this specification is, in fact, even more problematic since the presently used biodegradable materials do not always satisfy the requirement of degrading without harmful effects for, as we have seen (for example see Ref. [101]), the processes of degradation can be pro-inflammatory through the release of acidic moieties, residual catalysts and micron or sub-micron sized particles. What is urgently required is a reassessment of the specifications for these materials, which has to include a deeper understanding of their biocompatibility.

There will not be a single set of requirements for all of the applications, and they will depend on the tissue or organ under regeneration as well as the location of the regenerative process, that is whether the process is being carried out ex vivo or in vivo, and the nature of the bioreactor system. It should be obvious that the scaffold should have two functions, to determine the shape of the regenerated tissue and to facilitate the appropriate cell behaviour, especially the development and/or maintenance of phenotype and the expression of relevant extracellular matrix. Although cells seeded in a scaffold may regenerate tissue spontaneously without any specific guidance from the scaffold material, it is unlikely that this will be achieved with any degree of consistency and efficiency. The biomaterial should be biologically active in the sense that it should possess, within its molecular structure, the appropriate ligands that are recognisable by the relevant cells and made available to those cells with the right density and over the appropriate length of time. This is obviously a significant challenge, especially if more than one cell type is involved in every functional tissue in the body.

This will not be achieved with the conventional synthetic biomaterials, but should be possible with natural biopolymers, such as certain individual proteins (collagen [121], elastin [122], silk [123]), polysaccharides (hyaluronan [124], alginate [125], chitosan [126]), some natural tissue derived materials [127,128] and some engineered forms or derivatives of such substances [129]. It should be noted that there have been many attempts to confer this type of bioactivity to synthetic polymers by surface grafting of molecules, such as peptide or amino acid sequences [130]. Although some changes to properties in vitro are often seen, it is difficult to visualise how such a modified surface can maintain activity in vivo, especially as the underlying polymer has been designed to be hydrolysable. In order to facilitate the cell–surface interactions, certain properties will be important, including the hydrophilicity [131], and of special relevance will be the geometrical features of the porous structure, including the pore size and size distribution [132], the microarchitecture [133], and the degree of heterogeneity, isotropy and interconnectivity of the porosity within the template [134].

Of equal significance is the requirement for suitable biodegradation parameters. There is no point in designing a system that will facilitate complex tissue regeneration if that tissue is ultimately destroyed by the influx of inflammatory cells associated with the degradation process or if the material stimulates the immune system as it degrades and releases antigenic material. Obviously the material and its degradation products have to be devoid of any potential for mutagenicity, genotoxicity, carcinogenicity, reproductive toxicity and other adverse systemic effects.

It is clear that some basic principles of biocompatibility still apply, but that entirely different mechanisms of interaction should be required and achieved.

8. The central biocompatibility paradigm

We have previously defined biocompatibility in terms of the ability of a material to perform with an appropriate host response in a specific situation. That was, at its inception, a powerful reminder that biomaterials have to perform a function, and can only do so if they invoke a response from the tissues, or tissue components, that they are in contact with, that is, at the very least, compatible with that function, or better, actively support that function. It is necessary, as originally envisaged, to define biocompatibility specifically in relation to those functions, but also to have a more profound overarching concept. It is clear from some well established situations, in which there is ample clinical evidence, that the principal component of a material's biocompatibility is that, whatever the

Please cite this article in press as: David F. Williams, On the mechanisms of biocompatibility, Biomaterials (2008), doi:10.1016/j.biomaterials.2008.04.023

desired function, the material shall do no harm, just as the first principle of Hippocrates was that the doctor should do no harm. Long-term implantable medical devices are the obvious here, and the following definition or paradigm may be proposed:

The biocompatibility of a long term implantable medical device refers to the ability of the device to perform its intended function, with the desired degree of incorporation in the host, without eliciting any undesirable local or systemic effects in that host.

The edict that the biomaterial shall do no harm may well be reassuring to the recipient of an implantable device that is intended to survive longer than them, but may not be sufficient for other stakeholders in advanced medical technologies, where specific functionality, usually sooner rather than later, as well as safety is required. If we take tissue engineering scaffolds as examples, there is little point in using inert materials, or, even more importantly, materials that have non-specific or inappropriately directed activity. Here, it is suggested that a more appropriate paradigm would be:

The biocompatibility of a scaffold or matrix for a tissue engineering product refers to the ability to perform as a substrate that will support the appropriate cellular activity, including the facilitation of molecular and mechanical signalling systems, in order to optimise tissue regeneration, without eliciting any undesirable local or systemic responses in the eventual host.

We should recognise here that biomaterials are not essential for regenerative medicine. Regenerative medicine includes any therapy that aims to induce the regeneration of tissues or organs following disease or injury and may be achieved through gene therapy, cell therapy or tissue engineering, or a combination of these, any of which may be assisted by concurrent pharmaceutical intervention. In this context it is essential to recognise that the biomaterial will always be in a subservient role, and that the biocompatibility of that material is of paramount importance since, if they are not essential, or if they are of dubious safety, their existence will always be questionable.

The unified concept of biocompatibility is therefore as follows. A biomaterial is, by definition, foreign to the host, whether that be the recipient of a surgically invasive device, of a construct for the purposes of regenerative medicine, a drug or gene delivery entity or a vehicle to assist in diagnosis or imaging. Whatever the required function or purpose, the device or construct, and therefore the material of its construction, shall not produce any clinically significant adverse effects in the patient or host. However, the material should be expected to passively allow or actively produce demonstrable beneficial effects in that host, whether that be the stimulation of specific differentiation in stem cells, the positive assistance in the maintenance of cell phenotype, the facilitation of endothelialisation of intravascular devices or the pharmacological control of undesirable responses, such as intimal hyperplasia associated with intravascular stents and osteolysis associated with the release of wear debris from joint replacement prostheses.

We may therefore re-define biocompatibility as follows:

Biocompatibility refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy.

9. Conclusions

Our understanding of the mechanisms of biocompatibility has been restricted whilst the focus of attention has been long-term implantable devices. Here, over 50 years of experience has determined that, in the vast majority of circumstances, the sole requirement for biocompatibility in a medical device intended for sustained long-term contact with the tissues of the human body is that the material shall do no harm to those tissues, achieved through chemical and biological inertness. Rarely has an attempt to introduce biological activity into a biomaterial been clinically successful in these applications. Only now that the focus for biomaterials has turned towards tissue engineering, sophisticated cell, drug and gene delivery systems and indeed applications in biotechnology, has the need for specific and direct interactions between biomaterials and tissue components become necessary. The portfolio of biomaterials will now include poly(ethylenimine) nonviral vectors, recombinant silk, elastin and collagen proteins, superparamagnetic iron oxide nanoparticles, 3-D fibrinogen based hydrogels, RGD-polymer blends, electrospun nanofibrous composites, DNA-based nanoswitches for reagentless sensors and patterned, doped diamond like carbon for neuroprostheses, and many more. With these new biomaterials a new paradigm for biocompatibility has emerged. It is believed that once the need for this change is recognised, so our understanding of the mechanisms of biocompatibility will markedly improve.

Acknowledgements

This paper is based on many years experience at the University of Liverpool and I wish to acknowledge the support of many colleagues and students in Liverpool, too numerous to mention, over this time, and the financial support within UK, especially from the Research Councils EPSRC, BBSRC and MRC, and the European Commission, in particular for the STEPS project in the Framework VI Programme.

References

[1] Williams DF. Definitions in biomaterials. Amsterdam: Elsevier; 1987.
[2] Williams DF. The Williams dictionary of biomaterials. Liverpool: Liverpool University Press; 1999.
[3] Porter JA, von Fraunhofer JA. Success or failure of dental implants? A literature review with treatment considerations. Gen Dent 2005;53(6):423–32.
[4] Polikov VS, Tresco PA, Reichert WM. Response of brain tissue to chronically implanted neural electrodes. J Neurosci Methods 2005;148(1):1–18.
[5] Montanaro L, Campoccia D, Arciola CR. Advancements in molecular epidemiology of implant infections and future perspectives. Biomaterials 2007; 28(34):5155–68.
[6] Gorbet MB, Sefton MV. Endotoxin: the uninvited guest. Biomaterials 2005; 26(34):6811–7.
[7] Williams DF. The inert-bioactivity conundrum. In: Ellingsen JE, editor. The implant tissue interface. Boca Raton: CRC Press; 2003. p. 407–30.
[8] Jinno T, Goldberg VM, Davy D, Stevenson S. Osseointegration of surface-blasted implants made of titanium alloy and cobalt–chromium alloy in a rabbit intramedullary model. J Biomed Mater Res 1998;42(1):20–9.
[9] Puleo DA, Thomas MV. Implant surfaces. Dent Clin North Am 2006;50(3): 323–38.
[10] Lossdorfer S, Schwartz Z, Wang L, Lohmann CH, Turner JD, Wieland M, et al. Microrough implant surface topographies increase osteogenesis by reducing osteoclast formation and activity. J Biomed Mater Res A 2004;70(3):361–9.
[11] Hallab NJ, Anderson S, Stafford T, Glant T, Jacobs JJ. Lymphocyte responses in patients with total hip arthroplasty. J Orthop Res 2005;23(2):384–91.
[12] Purdue PE, Koulouvaris P, Potter HG, Nestor BJ, Sculco TP. The cellular and molecular biology of periprosthetic osteolysis. Clin Orthop Relat Res 2007; 454:251–61.
[13] Ingham E, Fisher J. The role of macrophages in osteolysis of total joint replacement. Biomaterials 2005;26(11):1271–86.
[14] Willert HG, Semlitsch M. Reactions of the articular capsule to artificial joint prostheses. In: Williams DF, editor. Biocompatibility of implant materials. London: Sector Publishing; 1976. p. 40–8.
[15] Goodman S. Wear particulates and osteolysis. Orthop Clin North Am 2008; 36(1):41–8.
[16] Ren W, Yang SY, Fang HW, Hsu S, Wooley PH. Distinct gene expression of receptor activator of nuclear factor-kappaB and rank ligand in the inflammatory response to variant morphologies of UHMWPE particles. Biomaterials 2003;24(26):4819–26.
[17] McKellop H, Shen FW, Lu B, Campbell P, Salovey R. Effect of sterilization method and other modifications on the wear resistance of acetabular cups

Please cite this article in press as: David F. Williams, On the mechanisms of biocompatibility, Biomaterials (2008), doi:10.1016/j.biomaterials.2008.04.023

made of ultra-high molecular weight polyethylene: a hip-simulator study. J Bone Joint Surg Am 2000;82-A(12):1708–25.
[18] Shanbhag AS. Use of bisphosphonates to improve the durability of total joint replacements. J Am Acad Orthop Surg 2006;14(4):215–25.
[19] D'Antonio J, Capello W, Manley M, Naughton M, Sutton K. Alumina ceramic bearings for total hip arthroplasty: five-year results of a prospective randomized study. Clin Orthop Relat Res 2005;436:164–71.
[20] Geesink RG, Hoefnagels NH. Six-year results of hydroxyapatite-coated total hip replacement. J Bone Joint Surg Br 1995;77(4):534–47.
[21] Tanzer M, Gollish J, Leighton R, Orrell K, Giacchino A, Welsh P, et al. The effect of adjuvant calcium phosphate coating on a porous-coated femoral stem. Clin Orthop Relat Res 2004;424:153–60.
[22] Ducheyne P, Qiu Q. Bioactive ceramics: the effect of surface reactivity on bone formation and bone cell function. Biomaterials 1999;20(23–24):2287–303.
[23] Dumbleton J, Manley MT. Hydroxyapatite-coated prostheses in total hip and knee arthroplasty. J Bone Joint Surg Am 2004;86(11):2526–40.
[24] Bauer TW, Schils J. The pathology of total joint arthroplasty. I. Mechanisms of implant fixation. Skeletal Radiol 1999;28(8):423–32.
[25] Astion DJ, Saluan P, Stulberg BN, Rimnac CM, Li S. The porous-coated anatomic total hip prosthesis: failure of the metal-backed acetabular component. J Bone Joint Surg Am 1996;78(5):755–66.
[26] Ohlin A. Failure of the Christiansen hip: survival analysis of 265 cases. Acta Orthop Scand 1990;61(1):7–11.
[27] Chevalier J. What future for zirconia as a biomaterial? Biomaterials 2006; 27(4):535–43.
[28] Nilsen AR, Wiig M. Total hip arthroplasty with Boneloc: loosening in 102/157 cases after 0.5–3 years. Acta Orthop Scand 1996;67(1):57–9.
[29] Jones CA, Beaupre LA, Johnston DW, Suarez-Almazor ME. Total joint arthroplasties: current concepts of patient outcomes after surgery. Clin Geriatr Med 2005;21(3):527–41.
[30] Steinert R, editor. Cataract surgery. Philadelphia: Saunders; 2003.
[31] Olson RJ, Mamalis N, Werner L, Apple DJ. Cataract treatment in the beginning of the 21st century. Am J Ophthalmol 2003;136(1):146–54.
[32] Elgohary MA, Hollick EJ, Bender LE, Heatley CJ, Wren SM, Boyce J, et al. Hydrophobic acrylic and plate-haptic silicone intraocular lens implantation in diabetic patients: pilot randomized clinical trial. J Cataract Refract Surg 2006;32(7):1188–95.
[33] Wejde G, Kugelberg M, Zetterstrom C. Posterior capsule opacification: comparison of 3 intraocular lenses of different materials and design. J Cataract Refract Surg 2003;29(8):1556–9.
[34] Hicks CR, Crawford GJ, Lou X, Tan DT, Snibson GR, Sutton G, et al. Corneal replacement using a synthetic hydrogel cornea, AlphaCor: device, preliminary outcomes and complications. Eye 2003;17(3):385–92.
[35] Crossley GH. Cardiac pacing leads. Cardiol Clin 2000;18(1):95–112.
[36] de Voogt WG. Pacemaker leads: performance and progress. Am J Cardiol 1999;83(5B):187D–91.
[37] Schubert MA, Wiggins MJ, Schaefer MP, Hiltner A, Anderson JM. Oxidative biodegradation mechanisms of biaxially strained poly(ether urethane urea) elastomers. J Biomed Mater Res 1995;29(3):337–47.
[38] Del Bufalo AG, Schlaepfer J, Fromer M, Kappenberger L. Acute and long-term ventricular stimulation thresholds with a new, iridium oxide-coated electrode. Pacing Clin Electrophysiol 1993;16(6):1240–4.
[39] Norlin A, Pan J, Leygraf C. Investigation of interfacial capacitance of Pt, Ti and TiN coated electrodes by electrochemical impedance spectroscopy. Biomol Eng 2002;19(2–6):67–71.
[40] Hua W, Mond HG, Strathmore N. Chronic steroid-eluting lead performance: a comparison of atrial and ventricular pacing. Pacing Clin Electrophysiol 1997;20(1 Pt 1):17–24.
[41] Washizuka T, Chinushi M, Kazama R, Hirono T, Watanabe H, Komura S, et al. Inappropriate discharges of intravenous implantable cardioverter defibrillators owing to lead failure. Int Heart J 2005;46(5):909–13.
[42] Eicken A, Kolb C, Lange S, Brodherr-Heberlein S, Zrenner B, Schreiber C, et al. Implantable cardioverter defibrillator (ICD) in children. Int J Cardiol 2006; 107(1):30–5.
[43] Van ZD, Heymans O. Breast implants: a review. Acta Chir Belg 2004;104(2): 158–65.
[44] Poeppl N, Schreml S, Lichtenegger F, Lenich A, Eisenmann-Klein M, Prantl L. Does the surface structure of implants have an impact on the formation of a capsular contracture? Aesthetic Plast Surg 2007;31(2):133–9.
[45] Marotta JS, Goldberg EP, Habal MB, Amery DP, Martin PJ, Urbaniak DJ, et al. Silicone gel breast implant failure: evaluation of properties of shells and gels for explanted prostheses and meta-analysis of literature rupture data. Ann Plast Surg 2002;49(3):227–42.
[46] Edworthy SM, Martin L, Barr SG, Birdsell DC, Brant RF, Fritzler MJ. A clinical study of the relationship between silicone breast implants and connective tissue disease. J Rheumatol 1998;25(2):254–60.
[47] Rosenberg NL. The neuromythology of silicone breast implants. Neurology 1996;46(2):308–14.
[48] Dush DM. Breast implants and illness: a model of psychological factors. Ann Rheum Dis 2001;60(7):653–7.
[49] Janowsky EC, Kupper LL, Hulka BS. Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. N Engl J Med 2000;342(11):781–90.
[50] Wolfram D, Rainer C, Niederegger H, Piza H, Wick G. Cellular and molecular composition of fibrous capsules formed around silicone breast implants with special focus on local immune reactions. J Autoimmun 2004;23(1):81–91.
[51] Adams TS, Crook T, Cadier MA. A late complication following the insertion of hydrogel breast implants. J Plast Reconstr Aesthet Surg 2007;60(2):210–2.
[52] Rizkalla M, Duncan C, Matthews RN. Trilucent breast implants: a 3 year series. Br J Plast Surg 2001;54(2):125–7.
[53] Kirkpatrick WN, Jones BM. The history of Trilucent implants, and a chemical analysis of the triglyceride filler in 51 consecutively removed Trilucent breast prostheses. Br J Plast Surg 2002;55(6):479–89.
[54] Klepetko W, Moritz A, Mlczoch J, Schurawitzki H, Domanig E, Wolner E. Leaflet fracture in Edwards-Duromedics bileaflet valves. J Thorac Cardiovasc Surg 1989;97(1):90–4.
[55] Hering D, Piper C, Horstkotte D. Drug insight: an overview of current anticoagulation therapy after heart valve replacement. Nat Clin Pract Cardiovasc Med 2005;2(8):415–22.
[56] Tornos P, Iung B, Permanyer-Miralda G, Baron G, Delahaye F, Gohlke-Barwolf C, et al. Infective endocarditis in Europe: lessons from the Euro heart survey. Heart 2005;91(5):571–5.
[57] Butany J, Leask RL, Desai ND, Jegatheeswaran A, Silversides C, Scully HE, et al. Pathologic analysis of 19 heart valves with silver-coated sewing rings. J Card Surg 2006;21(6):530–8.
[58] Bottio T, Thiene G. The changing spectrum of porcine bioprosthetic valve failure. Cardiovasc Pathol 2007;16(1):1–3.
[59] Gong G, Seifter E, Lyman WD, Factor SM, Blau S, Frater RW. Bioprosthetic cardiac valve degeneration: role of inflammatory and immune reactions. J Heart Valve Dis 1993;2(6):684–93.
[60] Schoen FJ, Levy RJ. Calcification of tissue heart valve substitutes: progress toward understanding and prevention. Ann Thorac Surg 2005;79(3): 1072–80.
[61] Human P, Zilla P. Inflammatory and immune processes: the neglected villain of bioprosthetic degeneration? J Long Term Eff Med Implants 2001;11(3–4): 199–220.
[62] Schmidt CE, Baier JM. Acellular vascular tissues: natural biomaterials for tissue repair and tissue engineering. Biomaterials 2000;21(22):2215–31.
[63] Rieder E, Kasimir MT, Silberhumer G, Seebacher G, Wolner E, Simon P, et al. Decellularization protocols of porcine heart valves differ importantly in efficiency of cell removal and susceptibility of the matrix to recellularization with human vascular cells. J Thorac Cardiovasc Surg 2004;127(2): 399–405.
[64] Simon P, Kasimir MT, Seebacher G, Weigel G, Ullrich R, Salzer-Muhar U, et al. Early failure of the tissue engineered porcine heart valve SYNERGRAFT in pediatric patients. Eur J Cardiothorac Surg 2003;23(6):1002–6.
[65] Dotter CT, Judkins MP. Transluminal treatment of atherosclerotic obstruction: description of a new technique and a preliminary report of its application. Circulation 1964;30:656–60.
[66] Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987;316(12):701–6.
[67] Wang K, Verbeken E, Mukherjee S, Zhou XR, De SI. Experimental evaluation of a new single wire stainless steel fishscale coronary stent (Freedom feminine). J Invasive Cardiol 1996;8(8):357–62.
[68] Cragg A, Lund G, Rysavy J, Castaneda F, Castaneda-Zuniga W, Amplatz K. Nonsurgical placement of arterial endoprostheses: a new technique using nitinol wire. Radiology 1983;147(1):261–3.
[69] Marrey RV, Burgermeister R, Grishaber RB, Ritchie RO. Fatigue and life prediction for cobalt–chromium stents: a fracture mechanics analysis. Biomaterials 2006;27(9):1988–2000.
[70] Serruys PW, Kutryk MJ, Ong AT. Coronary-artery stents. N Engl J Med 2006; 354(5):483–95.
[71] Luscher TF, Steffel J, Eberli FR, Joner M, Nakazawa G, Tanner FC, et al. Drug-eluting stent and coronary thrombosis: biological mechanisms and clinical implications. Circulation 2007;115(8):1051–8.
[72] Stone GW, Aronow HD. Long-term care after percutaneous coronary intervention: focus on the role of antiplatelet therapy. Mayo Clin Proc 2006; 81(5):641–52.
[73] Venkatraman SS, Tan LP, Joso JF, Boey YC, Wang X. Biodegradable stents with elastic memory. Biomaterials 2006;27(8):1573–8.
[74] Di Mario C, Griffiths H, Goktekin O, Peeters N, Verbist J, Bosiers M, et al. Drug-eluting bioabsorbable magnesium stent. J Interv Cardiol 2004;17(6):391–5.
[75] Mani G, Feldman MD, Patel D, Agrawal CM. Coronary stents: a materials perspective. Biomaterials 2007;28(9):1689–710.
[76] Muller KM, Dasbach G. The pathology of vascular grafts. Curr Top Pathol 1994;86:273–306.
[77] Lemson MS, Tordoir JH, Daemen MJ, Kitslaar PJ. Intimal hyperplasia in vascular grafts. Eur J Vasc Endovasc Surg 2000;19(4):336–50.
[78] Mamode N, Scott RN. Graft type for femoro-popliteal bypass surgery. Cochrane Database Syst Rev 2000;(2):CD001487.
[79] Lau H, Cheng SW. Is the preferential use of ePTFE grafts in femorofemoral bypass justified? Ann Vasc Surg 2001;15(3):383–7.
[80] Klinkert P, Post PN, Breslau PJ, van Bockel JH. Saphenous vein versus PTFE for above-knee femoropopliteal bypass: a review of the literature. Eur J Vasc Endovasc Surg 2004;27(4):357–62.
[81] Gorbet MB, Sefton MV. Biomaterial-associated thrombosis: roles of coagulation factors, complement, platelets and leukocytes. Biomaterials 2004; 25(26):5681–703.
[82] Salzmann DL, Kleinert LB, Berman SS, Williams SK. Inflammation and neovascularization associated with clinically used vascular prosthetic materials. Cardiovasc Pathol 1999;8(2):63–71.

Please cite this article in press as: David F. Williams, On the mechanisms of biocompatibility, Biomaterials (2008), doi:10.1016/j.biomaterials.2008.04.023

[83] Wahlgren CM, Sten-Linder M, Egberg N, Kalin B, Blohme L, Swedenborg J. The role of coagulation and inflammation after angioplasty in patients with peripheral arterial disease. Cardiovasc Intervent Radiol 2006;29(4): 530–5.
[84] Smith R, Oliver C, Williams DF. The enzymatic degradation of polymers in vitro. J Biomed Mater Res 1987;21(8):991–1003.
[85] Van Damme H, Deprez M, Creemers E, Limet R. Intrinsic structural failure of polyester (Dacron) vascular grafts. A general review. Acta Chir Belg 2005; 105(3):249–55.
[86] Shiiya N, Kunihara T, Matsuzaki K, Sugiki T. Spontaneous perigraft hematoma suggesting transgraft hemorrhage seven years after thoracic aortic replacement with a Dacron graft. Eur J Cardiothorac Surg 2006;30(2): 402–4.
[87] Pinchuk L. A review of the biostability and carcinogenicity of polyurethanes in medicine and the new generation of 'biostable' polyurethanes. J Biomater Sci Polym Ed 1994;6(3):225–67.
[88] Greisler HP. Arterial regeneration over absorbable prostheses. Arch Surg 1982;117(11):1425–31.
[89] Heyligers JM, Verhagen HJ, Rotmans JI, Weeterings C, de Groot PG, Moll FL, et al. Heparin immobilization reduces thrombogenicity of small-caliber expanded polytetrafluoroethylene grafts. J Vasc Surg 2006;43(3):587–91.
[90] Devine C, McCollum C. Heparin-bonded Dacron or polytetrafluoroethylene for femoropopliteal bypass: five-year results of a prospective randomized multicenter clinical trial. J Vasc Surg 2004;40(5):924–31.
[91] Walluscheck KP. Heparin-bonded expanded polytetrafluoroethylene vascular graft for occlusive vascular disease of the lower extremity. Ital J Vasc Endovasc Surg 2006;13(3):137–47.
[92] Peeters P, Verbist J, Deloose K, Bosiers M. Results with heparin bonded polytetrafluoroethylene grafts for femorodistal bypasses. J Cardiovasc Surg 2006;47(4):407–13.
[93] Frost MC, Reynolds MM, Meyerhoff ME. Polymers incorporating nitric oxide releasing/generating substances for improved biocompatibility of blood-contacting medical devices. Biomaterials 2005;26(14):1685–93.
[94] Cunningham KS, Gotlieb AI. The role of shear stress in the pathogenesis of atherosclerosis. Lab Invest 2005;85(1):9–23.
[95] Fillinger MF, Reinitz ER, Schwartz RA, Resetarits DE, Paskanik AM, Bruch D, et al. Graft geometry and venous intimal–medial hyperplasia in arteriovenous loop grafts. J Vasc Surg 1990;11(4):556–66.
[96] Meinhart JG, Deutsch M, Fischlein T, Howanietz N, Froschl A, Zilla P. Clinical autologous in vitro endothelialization of 153 infrainguinal ePTFE grafts. Ann Thorac Surg 2001;71(5 Suppl):S327–31.
[97] Zilla P, Bezuidenhout D, Human P. Prosthetic vascular grafts: wrong models, wrong questions and no healing. Biomaterials 2007;28(34):5009–27.
[98] Ali SA, Doherty PJ, Williams DF. Mechanisms of polymer degradation in implantable devices. 2. Poly(DL-lactic acid). J Biomed Mater Res 1993;27(11): 1409–18.
[99] Vert M, Mauduit J, Li S. Biodegradation of PLA/GA polymers: increasing complexity. Biomaterials 1994;15(15):1209–13.
[100] Bostman O, Pihlajamaki H. Clinical biocompatibility of biodegradable orthopaedic implants for internal fixation: a review. Biomaterials 2000;21(24): 2615–21.
[101] Bergsma JE, de Bruijn WC, Rozema FR, Bos RR, Boering G. Late degradation tissue response to poly(L-lactide) bone plates and screws. Biomaterials 1995; 16(1):25–31.
[102] Rokkanen PU, Bostman O, Hirvensalo E, Makela EA, Partio EK, Patiala H, et al. Bioabsorbable fixation in orthopaedic surgery and traumatology. Biomaterials 2000;21(24):2607–13.
[103] Qu XH, Wu Q, Zhang KY, Chen GQ. In vivo studies of poly(3-hydroxybutyrate-*co*-3-hydroxyhexanoate) based polymers: biodegradation and tissue reactions. Biomaterials 2006;27(19):3540–8.
[104] Shive MS, Anderson JM. Biodegradation and biocompatibility of PLA and PLGA microspheres. Adv Drug Deliv Rev 1997;28(1):5–24.
[105] Fournier E, Passirani C, Colin N, Sagodira S, Menei P, Benoit JP, et al. The brain tissue response to biodegradable poly(methylidene malonate 2.1.2)-based microspheres in the rat. Biomaterials 2006;27(28):4963–74.
[106] Le Visage C, Quaglia F, Dreux M, Ounnar S, Breton P, Bru N, et al. Novel microparticulate system made of poly(methylidene malonate 2.1.2). Biomaterials 2001;22(16):2229–38.
[107] Ignatius AA, Augat P, Hollstein E, Schorlemmer S, Peraus M, Pokinskyj P, et al. Biocompatibility and functionality of the degradable polymer alkylene bis(-dilactoyl)-methacrylate for screw augmentation in vivo. J Biomed Mater Res B Appl Biomater 2005;75(1):128–36.
[108] Grossterlinden L, Janssen A, Schmitz N, Priemel M, Pogoda P, Amling M, et al. Deleterious tissue reaction to an alkylene bis(dilactoyl)-methacrylate bone adhesive in long-term follow up after screw augmentation in an ovine model. Biomaterials 2006;27(18):3379–86.
[109] Bonzani IC, Adhikari R, Houshyar S, Mayadunne R, Gunatillake P, Stevens MM. Synthesis of two-component injectable polyurethanes for bone tissue engineering. Biomaterials 2007;28(3):423–33.
[110] Williams DF. The relationship between biomaterials and nanotechnology. Biomaterials 2008;29(12):1737–8.
[111] Donaldson K. Resolving the nanoparticles paradox. Nanomed 2006;1(2): 229–34.
[112] Hurst SJ, Lytton-Jean AK, Mirkin CA. Maximizing DNA loading on a range of gold nanoparticle sizes. Anal Chem 2006;78(24):8313–8.
[113] Efsing HO, Lindblad B, Mark J, Wolff T. Thromboembolic complications from central venous catheters: a comparison of three catheter materials. World J Surg 1983;7(3):419–23.
[114] Monreal M, Raventos A, Lerma R, Ruiz J, Lafoz E, Alastrue A, et al. Pulmonary embolism in patients with upper extremity DVT associated to venous central lines – a prospective study. Thromb Haemost 1994;72(4):548–50.
[115] van Rooden CJ, Tesselaar ME, Osanto S, Rosendaal FR, Huisman MV. Deep vein thrombosis associated with central venous catheters – a review. J Thromb Haemost 2005;3(11):2409–19.
[116] Brash JL. Exploiting the current paradigm of blood–material interactions for the rational design of blood-compatible materials. J Biomater Sci Polym Ed 2000;11(11):1135–46.
[117] Long DA, Coulthard MG. Effect of heparin-bonded central venous catheters on the incidence of catheter-related thrombosis and infection in children and adults. Anaesth Intensive Care 2006;34(4):481–4.
[118] Klement P, Du YJ, Berry LR, Tressel P, Chan AK. Chronic performance of polyurethane catheters covalently coated with ATH complex: a rabbit jugular vein model. Biomaterials 2006;27(29):5107–17.
[119] Williams DF, Atala A. The specifications for biomaterials in regenerative medicine. Nat Mater, in press.
[120] Williams DF. To engineer is to create: the link between engineering and regeneration. Trends Biotechnol 2006;24(1):4–8.
[121] Buttafoco L, Kolkman NG, Engbers-Buijtenhuijs P, Poot AA, Dijkstra PJ, Vermes I, et al. Electrospinning of collagen and elastin for tissue engineering applications. Biomaterials 2006;27(5):724–34.
[122] Simionescu DT, Lu Q, Song Y, Lee JS, Rosenbalm TN, Kelley C, et al. Biocompatibility and remodeling potential of pure arterial elastin and collagen scaffolds. Biomaterials 2006;27(5):702–13.
[123] Wang Y, Kim HJ, Vunjak-Novakovic G, Kaplan DL. Stem cell-based tissue engineering with silk biomaterials. Biomaterials 2006;27(36):6064–82.
[124] Hemmrich K, von HD, Rendchen R, Di BC, Milella E, Pallua N. Implantation of preadipocyte-loaded hyaluronic acid-based scaffolds into nude mice to evaluate potential for soft tissue engineering. Biomaterials 2005;26(34):7025–37.
[125] Gerecht-Nir S, Cohen S, Ziskind A, Itskovitz-Eldor J. Three-dimensional porous alginate scaffolds provide a conducive environment for generation of well-vascularized embryoid bodies from human embryonic stem cells. Biotechnol Bioeng 2004;88(3):313–20.
[126] Di MA, Sittinger M, Risbud MV. Chitosan: a versatile biopolymer for orthopaedic tissue-engineering. Biomaterials 2005;26(30):5983–90.
[127] Badylak S, Kokini K, Tullius B, Simmons-Byrd A, Morff R. Morphologic study of small intestinal submucosa as a body wall repair device. J Surg Res 2002; 103(2):190–202.
[128] Taylor PM. Biological matrices and bionanotechnology. Philos Trans R Soc Lond B Biol Sci 2007;362(1484):1313–20.
[129] Ando W, Tateishi K, Hart DA, Katakai D, Tanaka Y, Nakata K, et al. Cartilage repair using an in vitro generated scaffold-free tissue-engineered construct derived from porcine synovial mesenchymal stem cells. Biomaterials 2007; 28(36):5462–70.
[130] Chen R, Curran SJ, Curran JM, Hunt JA. The use of poly(L-lactide) and RGD modified microspheres as cell carriers in a flow intermittency bioreactor for tissue engineering cartilage. Biomaterials 2006;27(25):4453–60.
[131] Bhattarai SR, Bhattarai N, Viswanathamurthi P, Yi HK, Hwang PH, Kim HY. Hydrophilic nanofibrous structure of polylactide; fabrication and cell affinity. J Biomed Mater Res A 2006;78(2):247–57.
[132] Wu L, Ding J. Effects of porosity and pore size on in vitro degradation of three-dimensional porous poly(D,L-lactide-*co*-glycolide) scaffolds for tissue engineering. J Biomed Mater Res A 2005;75(4):767–77.
[133] Mastrogiacomo M, Scaglione S, Martinetti R, Dolcini L, Beltrame F, Cancedda R, et al. Role of scaffold internal structure on in vivo bone formation in macroporous calcium phosphate bioceramics. Biomaterials 2006; 27(17):3230–7.
[134] Moutos FT, Freed LE, Guilak F. A biomimetic three-dimensional woven composite scaffold for functional tissue engineering of cartilage. Nat Mater 2007;6(2):162–7.
[135] Pinchuk L, Wilson GJ, Barry JJ, Schoephoerster RT, Parel JM, Kennedy JP. Medical applications of poly(styrene-*block*-isobutylene-*block*-styrene) (''SIBS''). Biomaterials 2008;29(4):448–60.

Please cite this article in press as: David F. Williams, On the mechanisms of biocompatibility, Biomaterials (2008), doi:10.1016/j.biomaterials.2008.04.023