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Biomaterials and tissue engineering in reconstructive surgery

D F WILLIAMS

Professor of Tissue Engineering, The University of Liverpool, P.O.Box 147, Liverpool L69 3GA, UK
e-mail: dfw@liverpool.ac.uk

Abstract. This paper provides an account of the rationale for the development of implantable medical devices over the last half-century and explains the criteria that have controlled the selection of biomaterials for these critical applications. In spite of some good successes and excellent materials, there are still serious limitations to the performance of implants today, and the paper explains these limitations and develops this theme in order to describe the recent innovations in tissue engineering, which involves a different approach to reconstruction of the body

Keywords. Biomaterials; tissue engineering; biocompatibility; medical device.

1. Introduction

One of the most exciting and rewarding areas of advanced materials science research is that which involves the applications of materials to health care, and especially to reconstructive surgery. At a time when technological research should ideally contribute both to wealth creation and improvements to the quality of life, it is obvious that developments that lead to the implantation of advanced materials and devices within the body in order to treat disease and injury should have a very high priority. This paper attempts to place these clinical applications in the context of the expectations for medical devices, the performance of biomaterials and the relationship between materials science and the biology of the human patient.

Medical devices are used for a wide variety of purposes. Although there are several definitions of medical device, biomaterial, surgical material and so on (Williams 1999), they have primarily been written to assist lawyers and regulators to classify such objects and do not really help scientific and clinical understanding of the subject. It is better to describe the types of situation in which these materials and these devices are used in order to gain this basic understanding.

2. The clinical applications of biomaterials

There can be no doubt that the most widely recognised applications of biomaterials involve those situations where a tissue or organ has suffered from some disease or condition that has resulted in pain, malfunction or structural degeneration, and which can only be alleviated

by the replacement or augmentation of the affected part. The cause of the condition could be bacterial, viral or fungal, or could be related to an autoimmune, sclerotic, neoplastic or simply age-related process. The patients are often elderly but need not necessarily be so. They require that the pain is reduced or eliminated and that the offending tissue be circumvented by an alternative structure that is able to provide a degree of function compatible with the normal expectations of such a person. It may well be that this is best achieved by removal of the tissue and its replacement, but the objective may be better satisfied by introducing an additional functional component into the body that takes on the role of the affected tissue. For example the best solution to the arthritic hip may be to remove the affected bone and cartilage and replace them in their entirety with a total joint prosthesis, but with an atherosclerotic (i.e. blocked) artery, the objective may be more easily achieved with a by-pass rather than a replacement. The important thing is that the function is restored. It is, with a few exceptions, not necessary to make the prosthetic component look like or otherwise physically resemble the tissue that it is replacing, as long as it carries out the appropriate function. It follows on from this that it is a further, and indeed crucial, requirement that this prosthetic component is able to perform this function for as long as the patient is alive.

The main examples of this type of implantable device or prosthesis are joint replacements, vascular grafts that replace blood vessels, prosthetic heart valves, soft tissue (e.g. breast tissue) reconstruction prostheses, dental implants and restorative materials, and intraocular lenses for the treatment of cataracts (Williams 1982).

There are also those situations in which there is a malfunction of a tissue or organ and where relief may be obtained by the implantation of an engineering device that can assist the tissue or organ in its normal function. Typically such devices will be active, or powered, and will supply mechanical or physical energy to the affected part. Implantable electronic devices such as cardiac pacemakers, cochlear implants and defibrillators form a major group in this category, but they also include the powered systems that assist cardiac function such as the implantable heart pumps and ventricular assist devices. Such devices generally have three sections, the internal functional components such as a signal generator, power source and pumping chambers, the structures that house or contain such components, and the active interface between the device and the relevant tissues. The materials used for the internal functional components are not generally considered to be biomaterials since by definition they are not in contact with the tissues. However, the containment materials are crucial and are required to be diffusion barriers as well as mechanically robust and biostable, and to demonstrate excellent biocompatibility.

Some implantable devices are used to alter the shape, appearance or structure of the body. Breast implants are used more frequently for augmentation rather than post-mastectomy reconstruction. A wide variety of devices and materials are available for altering facial appearance, including bone augmentation and skin smoothing materials. Some of these reconstructive procedures are dramatic and ambitious, involving major movements of the bones in the cranium and fillings spaces between the fragments.

There are other situations in which control is required over regenerative processes in tissues and where a device is used either to enhance or repress tissue growth or proliferation. Spinal degeneration, for example, is usually treated by fusion of vertebrae and some cage systems are now available which incorporate materials (and sometimes ancillary drugs) that enhance the bone development that is required to produce the fusion. In another situation, stents are used within arteries and other tubular structures in order to maintain patency (that is, to keep the tube open) through the control of shape and the inhibition of endothelial and muscle tissue proliferation.

A further type of application is the transient implantable system that is directed towards the temporary support of traumatised or deformed tissues. This includes sutures, clips, adhesives and staples for soft tissues, haemostatic and sealant materials and devices in the vascular system, plates, screws, pins and fixators for bone fracture repair and devices in orthodontics for tooth movement. Sometimes these devices are directed towards the regeneration of new tissue rather than assisting a natural repair process. The regeneration of skin in areas of chronic ulcers or burns, and the regeneration of tendons and ligaments after sporting injuries are good examples. The requirements in these cases will be varied depending upon the stress transfer system within the device-tissue complex and on the desire for biostability or biodegradation.

Not all biomaterials are implanted within the body and there are several examples of medical devices that are used external to the body but which, nevertheless, come into critical contact with the tissues. These mostly involve external circulatory systems such as the heart lung machine used to support patients undergoing open-heart surgery, kidney dialysis machines and liver perfusion systems. These devices will have many components, often including tubing, blood reservoirs and heat exchangers in addition to the critical functioning component such as the dialysis membrane or the oxygenation membrane at which the exchange of metabolites or gases takes place.

This brief review of the current clinical applications of biomaterials indicates the extensive range of functions and properties that are necessary. Further reviews can be found in Bronzino (1995); Ratner *et al* (1996) and Wise *et al* (1995). It is not surprising that there are not just a few widely used biomaterials in clinical practice but rather a whole range of metals and alloys, ceramic and glasses, thermoplastics, resins, fibres, textiles and elastomers, composites and natural materials from which selection is made depending on the precise circumstances. The mechanical characteristics of a tissue replacement obviously have to bear some relationship to those of the host tissues. A comparison of the elastic constants and viscoelasticity of bone, arteries and skin suggest that replacement for these structures have to have very different mechanical characteristics. However, there is one set of overriding characteristics that control material selection within the body, and these are subsumed within the broad heading of biocompatibility, which is briefly reviewed next.

3. Biocompatibility

Biocompatibility is concerned with the interactions that take place between biomaterial and the tissue of the body. It is an enormously complex matter, involving a large number of mechanisms. It is intuitively obvious that since the human body does not normally contain foreign objects, such as large pieces of metal or plastic, and since evolution has determined that the body has exquisitely refined capabilities to defend itself against invasion, for example by bacteria, we should expect there to be a strong inherent capacity to respond aggressively to implanted medical devices. In the early stages of biomaterials development, there was only one major thought lying behind any decision to use a material on the basis of biocompatibility, which was that the material should do the patient no harm. This implied that the material should not interact with the body but merely reside in the body, carrying out its intended function without either being affected by the tissues or having any influence on those tissues. Early papers on the selection of biomaterials would set out the criteria in terms of a series of negatives such that the material should be inert and non-toxic, non-irritant, non-thrombogenic and so on. At this time this was a sensible position and led, as we shall see, to the emergence of several materials that gave good performance in a range of devices, such as titanium, carbon and silicone elastomers (Williams 1981).

It was, however, naïve to believe that anything could be placed in the human body without there being any interaction between the material and the tissue. Whilst it is certainly true that good performance has been achieved with a limited number of materials in a limited number of applications, there have been many other situations where success has been very hard to achieve on this basis. It is necessary therefore to consider the principles of these interactions in order to understand the rationale of the selection of biomaterials today, and the rationale of a somewhat different approach to reconstructive surgery. It is worth bearing in mind the currently accepted definition of biocompatibility, which is 'the ability of a material to perform with an appropriate host response in a given situation' (Williams 1999). This definition emphasises the positive nature of the interactions. It allows for the act that the most appropriate situation may be inertness and non-recognition, but also implies that interactivity between the material and the host could be positively encouraged and directed in a way that is the most beneficial for the functionality and retention of the device.

Biocompatibility is not controlled by one process but is the sum of many different processes. There are two compartments in this system, the material and the host tissue, and it is usual to consider the reactions that occur within these separate parts. It is also important, however, that the phenomena within these two components are often mutually interdependent, and that there is an interface between them, which plays a crucial, of often subtle, role in the developing process (Kasemo & Lausma 1986).

3.1 *Interfacial phenomena*

As soon as a biomaterial is placed in contact with tissues, certain molecules dissolved in the fluid phase of that tissue are adsorbed onto the biomaterial's surface. An adsorbed protein layer is established within minutes, and a dynamic process of adsorption, desorption and exchange takes place within this region. These processes are perfectly understandable: the biomaterial surfaces are usually of relatively high surface energy and tissue fluids can be considered as solutions supersaturated with molecules such as proteins, glycoproteins and polysaccharides. It is inevitable from simple thermodynamic reasoning that some of these molecules will adsorb onto the high-energy surfaces, but the situation is complex since there are so many types of macromolecule in solution in blood, plasma and extracellular fluids, with quite varying concentrations and affinities and adhesiveness. This explains why some proteins of low concentration, such as laminin, fibronectin and vitronectin have a high affinity for biomaterials surfaces, since they are naturally adhesive molecules, whilst albumin and haemoglobin have low affinity in spite of much higher concentrations. On the material side, a number of surface characteristics are influential in determining adsorption and desorption profiles, including surface energy, charge, water content and hydrophilicity, surface roughness and surface chemistry, but clear unambiguous relationships between any one surface parameter and any one adsorption parameter are difficult to define (Norde 1986; Curtis & Wilkinson 1997).

There are several important consequences of these interfacial reactions. First, the adsorption of a protein or similar molecule nay cause a profound change to its properties, which can under some circumstances lead to major physiological events. The change to the shape of certain plasma protein molecules after adsorption can be the initiating event in the formation of a blood clot or the development of a profound response from the immune system, for example. Secondly, whilst the layer of protein may be only of monomolecular dimensions, its presence means that the rest of the body does not come into contact with the native biomaterial surface again. The interactions between cells and materials, which really control biocompatibility actually takes place via a layer of proteins.

3.2 *Material stability*

As noted before, most biomaterials have been selected on the basis of their inertness, which in this context implies a resistance to degradation. This again is a very complex matter since there are so many active substances and components of the physiological environment that have the potential to interact with and ultimately degrade material surfaces. A few important general features may be identified here in the context of the overall contribution of material degradation to biocompatibility. Material degradation can have two broad consequences for medical devices. First degradation of a material can result in loss of structural integrity of a device, possibly with its ultimate dissolution or removal. This may be undesirable in the case of a device designed to be inert, but could be desirable in those devices which are intentionally biodegradable. Secondly, the release of products of the degradation process may affect the tissues, either locally or systemically, and either adversely, when unintended, or possibly beneficially when the released products have desirable and intended biological functions.

The release of components from biomaterials may take many different forms. With a metal, it may involve the release of soluble metal ions or particulate corrosion products. With a polymer, it may involve small molecules resulting from depolymerisation, fragments of polymer arising from heterogeneous degradation or the release, through leaching processes, of additives and residual catalysts. Any of these components released into the tissue can have an effect on that tissue, and clearly this can take place over a prolonged period of time. Of considerable significance is the fact that the degradation process and the response of tissues to the degradation products are highly interdependent. Although tissues are often thought of as saline solutions as far as reactivity with synthetic materials is concerned, they are far more complex than that, and it is the precise nature of the tissue environment that controls the degradation process. In particular, the key feature of the tissue in the response to a degrading material is inflammation (Hunt *et al* 1995). Inflammatory cells tend to produce a variety of active species, such as free radicals, peroxides and superoxides and enzymes, all of which are able to influence or even initiate material degradation. Since it is the presence of the material itself and its corrosion or degradation products that are instrumental in aggravating the inflammatory cells, and since these cells become more aggressive to materials than the normal extracellular fluid, the process is likely to become autocatalytic.

3.3 *The host response*

Biomaterials are normally implanted into sites that are already compromised by disease and trauma. The sequence of events in the host associated with the procedure will normally be the excision or manipulation of the affected tissue or organ, the physical implantation of the material into the appropriate site, the healing of the tissues at that site and the functional incorporation of the device within the host. The response of the host to the device therefore involves far more than is associated with the mechanism of cell-material or extracellular matrix molecule - material interactions that take place at the interface. There are many mediators of the local host response, it being recognised in particular that the tissue will inevitably be traumatised by the implantation procedure, such that the specific response to the material has to be superimposed upon the response to trauma. Under ideal conditions the wounded tissue should heal quickly and uneventfully, leaving the biomaterial in a zone of repair tissue, the morphology of which should not change very much subsequently. In reality, several factors combine to ensure that some further changes do take place under most circumstances. The natural ageing process in the host and time dependent structural changes in the tissue will have some impact, but the most important factors are the influence of components released

from the material into the tissue, as discussed above, and the mechanical disturbances to the host caused by the presence of the device.

The host response therefore reflects a balance between repair and inflammatory processes. Immediately following surgical trauma, the blood vessels in the vicinity dilate in the first stage of acute inflammation, the local blood flow increasing and white blood cells passing into the local tissue. The dominant white cells are the leukocytes, particularly the polymorphonuclear leukocytes, or neutrophils. It is unlikely that the material per se will have any influence over this acute phase since it is the general insult to the tissue that is responsible for the reaction. These cells release a variety of molecules, including histamine, which are chemoattractive, causing large numbers of other inflammatory cells to be attracted to the site, especially macrophages. In the absence of infection, and provided the biomaterial is reasonably inert and not overtly toxic, the inflammatory response will be dominated by this normal defensive behaviour of neutrophils and macrophages. Simultaneous with this inflammatory process, fibroblasts are attracted to the area in order to begin the process of tissue repair in which they are active in synthesizing and releasing collagen. Collagen is produced quite quickly, and in a matter of days it will have restored continuity across the injured site, the strength of the tissue constantly increasing as the collagen cross-links. At the same time, damaged blood capillaries start to regenerate in order to re-establish vascularity. Thus, a wound containing an inert implant will heal by the formation of a zone of vascularised fibrous tissue that envelops the implant, and it would be expected that the inflammation would have subsided within a few weeks. This is the classical picture of the fibrous encapsulation of biomaterials or medical devices, and if no other events took place and no other factors intervened, this capsule would remain in this form for as long as the implant was in the tissues.

In reality, the tissue response is likely to be more extensive than portrayed in this model, a greater response involving either or both a thicker capsule or the development of a chronic inflammation. A thicker fibrous capsule normally results from mechanical interference since relative movement between the material and the surrounding tissue is a stimulus to fibrogenesis, that is the production of fibrous tissue by fibroblasts. In this context, the surface roughness of the material may have an influence on the host response over and above that associated with cellular recognition of surface features. In practice there may be two competing events taking place. An irregular rough surface may provoke greater fibrosis simply because of the greater mechanical irritation provided by the surface asperities. On the other hand, the fibrous tissue that does form in the immediate post-operative phase may conform to those geometrical features, thereby providing a form of interlocking and reducing relative movement.

There are several ways in which a material surface could influence the progress of inflammation. The first involves the adsorption and desorption events that take place at the interface, as noted earlier. It is not expected that inflammatory cells such as macrophages have receptors for synthetic materials; receptors are the specific molecular structures on cell membranes that bind very selectively to molecules in the tissue, thereby stimulating a biochemical process. However, just as these inflammatory cells normally recognise and intercept bacteria or other organic debris by virtue of the molecular structure on their membranes that interact with the receptors, it should not be surprising that a protein covered biomaterial surface could similarly activate an inflammatory cell. More importantly, as already noted, it is the release of some components from the material surfaces that can influence the inflammation. A large variety of substances can be released, either from the degradation process outlined earlier, or through other effects such as wear. These substances range from highly mobile and active ionic species to particulate inert substances. They include fillers and fibre fragments from composites, polymeric and ceramic wear debris from joint replacement prostheses, metal ions

and compounds, antioxidants and lubricants, residual catalysts, exfoliated grains from oxide ceramics and so on. Inevitably, the release of any component from a biomaterial is likely to be associated with increased inflammatory activity.

Macrophages are probably the most important phagocytic cells in this situation. These cells are extremely efficient scavengers of small particulate matter, any particle ranging from tens of nanometres to 10 micrometres in diameter being readily engulfed, or phagocytosed. If macrophages encounter particles larger than this they have the capacity to fuse together to form giant cells. Once ingested by a macrophage or a giant cell, a foreign particle will stimulate metabolic activity within the cell, the products of such activation including free radicals and other active oxidising species. The lysosomes within the cell also become active and synthesis enzymes that may be used in an attempt to degrade or digest the foreign substance. An activated inflammatory cell is therefore a minute focus of intense biochemical activity, primarily directed at the repulsion of the invading substances. Because of the need for inflammatory cells to deal with invading bacteria on a routine basis, and because such organisms have the capacity to multiply at a rapid rate, the defence mechanism has evolved such that it does not rely upon chance meetings between macrophages and bacteria. During the process of activation, the cells synthesise and secrete a wide variety of signalling molecules, which are responsible for attracting other cells to the area and stimulating other phases of the defence process. These molecules include the family of substances known as cytokines, which are important markers of the intensity of inflammatory reactions to biomaterials.

An extensive chronic (i.e. prolonged) inflammatory response may have a number of consequences. In many cases, a histologically identifiable chronic response may have no perceptible clinical manifestation. At the other extreme, a cellular and fluid infiltrate may give rise to swelling, local pain and even tissue death. In between these two ends of the spectrum, the inflammation may itself stimulate more repair so that excessive fibrosis occurs, whilst the extended response may interfere with implant function.

This brief overview of some of the important mechanisms and mediators of biocompatibility has served to highlight the complexity of the phenomena and the nature of some of the factors that control materials selection. It should be said that there are many other biocompatibility phenomena, such as thrombogenicity, carcinogenicity, reproductive toxicity and genotoxicity that this discussion has been unable to address.

4. The evolution of biomaterials

With the general nature of medical device applications in mind, and a knowledge of the principles of biocompatibility, we can now address the rationale for the selection of biomaterials. It was the reconstruction of broken limbs that started to generate serious interest in biomaterials over a century ago. Bearing in mind that plastics and engineering ceramics had not been invented then, it was iron and steel that the early pioneers turned to. With bone fracture plates, carbon steel, then vanadium steel and later stainless steel were utilised in turn, the medical applications following on some years behind the introduction of such material into broader engineering applications. There was a perception that an implant had to be strong enough to sustain the body's functional stresses for an appropriate length of time without falling apart or having an adverse effect on the patient. This principle was to control the choice of materials for a multitude of medical applications for decades to come. Maintain structural integrity and do not irritate the host were the predicates of biomaterials selection. There are two significant features about this position that have had a considerable bearing on the development of biomaterials since then. The first is that no one really knew what features of a material

controlled whether it fell apart or not. The second was that no one really knew what it was about a material that caused it to irritate the host. We have only recently begun to understand the phenomena, outlined earlier, that control the material – tissue interactions, and much of the history of biomaterials selection has taken place in ignorance of the underlying science.

With respect to the first point, it was assumed at the time that the criteria that controlled the degradation of materials in general industrial or domestic situations also controlled the performance of materials in the body. The fact that today we know that that a piece of coral which existed in the ocean for centuries will be broken down, resorbed and metabolised within months of being placed in the body suggest that this assumption was not necessarily valid.

With respect to the second point, the unknown relationship between the dose-response toxicology of implanted materials and the effects of parenteral administration of components of the material, coupled with the complexity of the mechanisms by which implanted materials can affect the host, make an unequivocal correlation between the presence of a material and the host response almost impossible to determine. The fact that a carbon steel nail used to treat a fracture of the ankle of a soldier in the First World War in 1918 only exerted an adverse effect in that person when corroded fragments spontaneously extruded though the skin without warning some 60 years later again suggest that the matter is not simple.

The intuition of the first surgeons and engineers working in this area that, in spite of not knowing these complex mechanisms, it was better to use metals and alloys that were as inert as possible coloured this evolution over the next fifty or so years. Stainless steel was the dominant surgical material by the 1930's but this was then supplemented by some cobalt alloys that had been developed for aerospace use. Over the ensuing decades the specifications for both stainless steel and cobalt chromium for medical use were improved and refined, eventually producing a portfolio of applications ranging across the whole spectrum of surgical disciplines. All of these alloys were based upon the corrosion resistance provided by the passivity associated with the chromium content, their mechanical properties varying with the underlying metallurgical structure, itself controlled by composition and thermomechanical treatments.

In the 1960's there emerged a competitor to these chromium based corrosion resistant alloys in the form of titanium, which showed extremely good corrosion resistance and biocompatibility. The commercially pure metal did not have the requisite mechanical properties for many of the demanding orthopaedic applications, but the introduction of the two phase alloys, especially the titanium - 6% aluminium - 4% vanadium addressed this difficulty. Applications in spinal surgery, pacemaker cans, heart valves and dental implants soon followed. Occasionally there has been a need for functionality other than mechanical performance, for example devices requiring specific electrical or magnetic properties. In most cases, the platinum group metals, primarily platinum itself or alloys of platinum with palladium or iridium, have been used. Other noble metals, primarily gold and silver have also found some medical applications.

The situation with regard to metallic materials at the beginning of the twenty first century, therefore is not that much different to that which prevailed in the 1970s. There are variations in specifications, but these represent relatively minor evolutionary changes. There has been one substantial difference with respect to this portfolio of alloys, involving the introduction of shape-memory alloys, and in particular Nitinol, a nickel-titanium alloy. This has been used in a number of orthodontic and orthopaedic procedures, but it has largely become known for its use in intravascular stents, where the shape memory effect allows for the catheter based delivery of expandable stents to the site of a lesion and its subsequent expansion to reinforce the vascular wall after release from the catheter. This represents an interesting perspective on

the general use of metallic biomaterials today, since their use has probably peaked as surgeons move away from the monolithic replacement of parts of the body towards the less invasive reconstructive procedures, with 'smart' or 'intelligent' materials being far more appropriate.

In general, the use of metals is on the decline. It has always been illogical to replace or augment tissues with metals, but for a long time there have been no alternatives. Tissues are cellular, heterogeneous, anisotropic, aqueous and viable. Metals are acellular, relatively homogeneous and isotropic, anhydrous and hydrophobic, and dead. In recent years, two alternative approaches to this situation have emerged. The first involves the use of more natural materials for the construction of implantable medical devices, and the second moves away from manufactured, traditional engineering structures for tissue replacement to an approach which involves using structures and techniques that facilitate tissue regeneration, the area that has become known as tissue engineering. We shall deal with these two areas in turn.

As implied above, at the time when implants were first being developed, there were very few alternative engineering materials to which implant designers could turn. Fortunately, as attempts were made to create medical devices other than those for load bearing applications in orthopaedics, the plastics industry was just commencing the first phase of the invention of some radically new types of materials. The new plastics were based on synthetic polymers, which were designed as macromolecular structures that emulated to a certain extent some natural materials, but which possessed considerably enhanced mechanical properties and durability. The search for such materials, initially intended for a variety of industrial applications, is exemplified by the rationale for the development of nylon fibres. In the 1930's it had been recognised that some molecules could be synthesised with very similar structures to those of natural materials such as wool and silk. The initial form in which these synthetic analogues of the natural polymers was not very attractive for engineering applications, but these soon followed as the invention of nylon led to the evolution of a variety of polymers and structures such as fibres and textiles, and these were soon put to good use in implantable devices. Nylons themselves, as polyamides, are not the perfect textiles for implantation because they have hydrolysable bonds and degradation occurs sooner or later. In fact it still remains a significant problem to try to develop textiles for long-term implantation with appropriate biostability, since so many of the molecular structures that are ideal for the processing steps for the production of fibres are susceptible to ageing and degradation. Nevertheless, with the development of polymers such as the aromatic polyesters, including polyethylene terephthalate, made available in the form of the textile Dacron, there were sufficiently good characteristics for certain medical applications to be contemplated, and by the 1950's a variety of such uses including the replacement of blood vessels, were already in clinical practice.

Not all applications of polymers for implantation arose from the desire to have greater similarity to the structural characteristics of tissues. In some situations it was simply that the structure of metals could not possibly provide the functional behaviour of the device in question. The best examples here are those that involve the treatment or correction of disorders of the eye, where it is clearly impossible to sustain light transmission if an opaque piece of metal were to be placed in the eye. It was fortuitous that one of the most successful of all plastics ever developed is transparent and ideally suited to a number of critical applications involving replacement of ocular tissue.

Polymethylmethacrylate is one of the simplest of all polymers and is highly transparent because of its totally amorphous structure. Intraocular and contact lenses have been made from either PMMA itself or from other members of the acrylic family, especially the polyhydroxyethylmethacrylate, widely used as a soft water-containing contact lens material. Some

of these acrylics have also had a marked influence on the development of biomaterials, not so much because of intrinsic functional properties but more because of their ability to be fabricated in situ. The polymerisation of methyl methacrylate under ambient conditions has led to the adaptation of the material for in situ curing of bone cements and a variety of dental appliances.

The fact that synthetic polymers may have characteristics more similar to the natural polymers of tissue does not guarantee success in medical applications and indeed, over the years there have been many concerns about the biocompatibility of these polymers such that the actual number in medical use as parts of manufactured medical devices is not as significant as once predicted.. Two features of commercial polymers have served to limit their use, and determine the overall direction of development. The first is that almost all polymeric structures are susceptible to some form of ageing, often in the form of molecular degradation. Implants intended for long-term use in the body are unlikely to achieve clinical success if they breakdown or otherwise deteriorate during their design life. Thus, the tendency to suffer hydrolytic degradation has restricted the use of many otherwise highly appropriate materials, including a variety of polyamides, polyesters and polyurethanes. Similarly, a tendency towards oxidative degradation has provided limitations to the performance of polymers such as the polyolefins (including polyethylene and polypropylene).

The second generic limitation to the medical uses of polymers relates to the fact that the polymers themselves are rarely usable in pure form. This arises either because the pure macromolecule has characteristics that are unacceptable and have to be modified through the use of various additives, or because it is impossible to remove contaminants or residues from the material during or after the processing. Whilst the biocompatibility of a pure macromolecule may be extremely good with respect to many clinical applications, these characteristics are almost invariably compromised by the presence of additives or residues which, by their very nature, are usually extractable by the physiological environment. Polyvinylchloride (PVC) provides a good example since in pure form it is a rather unattractive material, being hard and brittle, but the addition of significant quantities of a plasticizer renders the material flexible and tough so that it is ideal for many medical uses, including catheters, drains, tubing and blood bags.

The need for polymers that were as inert as possible and substantially free of additives and contaminants led to the emergence of a small group of materials in the 1960's that were to play an immensely significant role in the development of implantable devices. Probably the most inert of all polymers is polytetrafluoroethylene (PTFE) and this has been shown to have excellent biocompatibility under many different circumstances. It does not have very good mechanical properties, which limits the stressed applications, but in the form of expanded PTFE, most widely known commercially as GoreTex, it has found widespread use in the vascular system and areas of soft tissue reconstruction. A further inert polymer to find extensive use in medical devices is polydimethylsiloxane, which is available in a variety of forms including elastomers gels and fluids, some of these finding extensive applications in soft tissue reconstruction, especially breast implants. A third very stable polymer with strong biomedical connections is polyethylene. Although as noted above it can suffer oxidation, it does have some very interesting properties, which have led to its use as bearing surfaces in total joint replacements.

These are some of the main examples of polymeric materials used in implantable devices. There are many others, some of which have very restricted applications, including a range of biodegradable aliphatic polyesters such as polylactic acid and a range of engineering thermoplastics such as polyetheretherketone and polysulphone. The search for better and

more appropriate polymers for implantation has not been straightforward and a variety of scientific and logistic difficulties has restricted these developments.

This discussion has concentrated on metals and polymers. Space does not allow a discussion of other classes of biomaterial, and it should be recognised that a group of ceramics, glasses, carbons and composites are also used. The developments seen with these materials largely parallel those seen with the metals and polymers, although it is fair to say that the introduction into medical use of many of the advanced materials of the late twentieth century has not been very significant.

5. Tissue engineering

We now move on to the final part of this story, which concerns the emergence of the subject that has come to be known as tissue engineering. We may summarise the discussions above by concluding that the developments in clinical expertise and the engineering quality of medical devices during the last thirty years has led to considerable success and effectiveness of trauma repair and tissue replacement. In spite of this success however, the whole field of implant surgery is witnessing a gradual shift away from the robust maximally invasive approaches in the treatment of disorders and injuries towards the use of the less invasive techniques that attempt to encompass biological or physiological concepts of tissue repair.

The concept of tissue engineering is best seen as an alternative to transplantation. In many areas of medicine, one of the most appealing solutions to irretrievable organ or tissue failure has been that of transplantation, using tissues and organs from donors. The donors could be the patients themselves, as with skin grafting, live immunologically matched humans, as with bone marrow transplants, deceased human donors as with heart transplants, or possibly animals. Whilst many of these procedures using transplanted tissues are very successful, as with, for example, corneal transplants and porcine heart valves, there are clear limitations and difficulties. These start with the obvious immunological problems associated with the use of foreign proteins, which means that recipients of viable organ transplants have to be immunologically suppressed, whilst xenogeneic tissues (from animals) have to be rendered non-immunogenic by chemical means. Added to these problems are those of the ethics and logistics and those of the potential for transmission of infectious agents, including retroviruses and prion proteins

There are solutions to many of these problems on the horizon, with, for example, the use of transgenic animals or cloning, but there are significant political and ethical issues to resolve before the undoubtedly feasible technological progress can be seen. It is here that the full potential for tissue engineering can be seen. The critical issue in treating compromised tissue is the need to replace or repair tissue that, for some reason is unable to perform its normal function but which does not itself have the power, or at least sufficient power, to regenerate itself. Some tissues have considerable powers of repair and regeneration in the adult human, such as skin and bone. In other cases, for example muscle and nerve, the ability to repair is very limited indeed. What is required is a facility or technique to persuade compromised tissues to regenerate themselves. Instead of taking sections of tissues from donor sites, it may be more logical to identify and isolate those active components of tissues that are responsible for tissue regeneration and provide them with the right environment and optimal conditions for them to stimulate this tissue regeneration.

Today, therefore, we have on the one hand the conventionally engineered implantable medical devices, which have significant limitations from the performance and durability point of view, in spite of some excellent biomaterials, and on the other hand we have transplanted

tissues which also have limitations but which might be more effective if their active components could be used differently. Tissue engineering fills the gap between these two approaches. The concept is to take a suitable material that can give physical form or outline to the area of tissue to be regenerated and to invest it with those tissue components that are responsible for tissue growth and repair. The combination, often called a construct, is able to help the patient regenerate new functional tissue. The tissue components may be cells or biomolecules or both. On the basis of this analysis, a definition of tissue engineering has been produced as follows' tissue engineering is the persuasion of the body to heal itself through the delivery to the appropriate sites of molecular signals, cells, and /or supporting structures.

The most common type of tissue engineering product is one which involves a biodegradable polymeric support (for example in the form of a porous scaffold) into which are introduced cells of the appropriate phenotype, along with some suitable drugs such as growth factors. This construct may be cultured in a sterile bioreactor, when the cells produce the regenerated tissue, which can then be implanted in the host. This is a very ambitious objective and only limited success has been achieved so far in relatively simple areas such as the skin. Developments are well advanced in bone and cartilage regeneration, and there is much activity in experimental systems for arteries and nerves. A variety of materials have been considered for the scaffolds (Hubbell 1995) the most common being the biodegradable polyesters mentioned previously and some natural biopolymers such as collagen and a variety of polysaccharides.

6. Conclusions

This review of biomaterials, medical devices and tissue engineering has attempted to demonstrate the very significant progress that has been made with the use of advanced materials within the human body. It will be clear from the discussions, however, that the human body is a very complex place, with an aggressive and unforgiving nature, and it is not surprising that there is still a long way to go before we can readily, routinely and successfully intervene and correct nature's mistakes.

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