CHAPTER 1

Synthetic Materials in Medicine

1 Introduction

The use of synthetic materials in the body by medical and dental practitioners to provide repair and function has grown remarkably in the last 30–40 years, though the concept of using such artificial materials is very old. For example, Plaster of Paris was pioneered as bone-substitute material towards the end of the nineteenth century, and dental fillings, including amalgam, have been around for well over 150 years. The use of engineered structures fabricated from metals and polymers in orthopaedic surgery has a more recent history, however, beginning with Dr (later Sir) John Charnley's work on the replacement of arthritic hips in the early 1960s.[1,2] This surgical repair technique, known as total hip arthroplasty, has seen particularly spectacular growth, and since Charnley's original cemented hip replacements there have been a variety of new materials and new designs for implantable devices, and these are now available not only for hips, but also for knees, toes and fingers.

Synthetic materials used in the body in this way are widely referred to as *biomaterials*. This use of the term appears to have originated in 1967 with the first 'International Biomaterials Symposium' at Clemson University, South Carolina, since which time it has been used extensively in this way. In many ways to apply the word *biomaterials* to synthetic materials is not very satisfactory since by analogy with, for example, the word biochemistry, it might be assumed to refer to materials of biological origin. However, within the field of implantable devices, the word *biomaterial* has been formally defined as *a non-viable material used in a biomedical device intended to interact with biological systems*.[3] This definition was adopted at the Consensus Conference of the European Society for Biomaterials, held at Chester, UK, in March 1987, and has been widely accepted ever since. In fact, some sort of definition of this type was already implicit in the title of the organisation which ran the meeting, the European Society for Biomaterials, because the Society's object from the time it was established in 1976 was to promote the study the science of such synthetic materials. It was never primarily concerned with the science of natural substances, such as teeth or bones. The current definition was also

implicit in the title of the scientific journal *Biomaterials*, which was first published in 1980. Whatever the rights and wrongs of the etymology, by usage the term *biomaterial* has now clearly come to mean a synthetic material with a biological destination rather than a biological origin.

There is a further caveat with the term, in that it is usually applied to materials designed to reside within the body for some considerable time. Thus, materials used to fabricate devices used only in surgery, ranging in sophistication from sensors to catheters, are not usually regarded as biomaterials. They may interact with a biological system, the body, but such interaction is usually relatively brief. Sutures, too, are not usually regarded as biomaterials for a similar reason. On the other hand, degradable polymers of the type used in sutures are finding increasingly novel uses in medicine, for example as temporary scaffolds and supports for bone immobilisation. These enable the body's own repair mechanisms time to bring about complete healing without premature loading and potential failure and under these circumstances, the polymers become biomaterials, because their interaction with the body must continue for a considerable time.

The field of biomaterials science encompasses all classes of material, *i.e.* polymers, ceramics, glasses and metals, and a wide range of branches of surgery: dental, ophthalmic, orthopaedic, cardiovascular and so on. The key requirement of any material or combination of materials used in the body is that, in addition to providing mechanical support or repair, it should be *biocompatible*. The subject of biocompatibility is covered in detail in Chapter 6, but at this stage we should note its definition. This is *the ability of a material to perform with appropriate host response in a specific application.*[1] As stated in this definition, biocompatibility is not a property of a material *per se*; the material needs to elicit an appropriate response, and whether such a response is appropriate will depend on the site in the body at which it has been placed. A material which shows excellent biocompatibility, for example, in contact with bone would not necessarily show good biocompatibility when used in a blood-contacting device, such as an artificial heart valve. Thus the location within the body is as important in determining whether a material is biocompatible as the composition of the material.

The property of biocompatibility is distinct from that of inertness, which would imply a complete absence of response from the body. At one stage, it was thought that inertness was a desirable property, but nowadays inertness is not thought possible. Even materials which seem inert in most technical applications, such as polytetrafluoroethylene, PTFE, prove to be highly active when placed within the body. PTFE was once used to fabricate the acetabular cups used in experimental hip replacement surgery.[4] When used in conjunction with a metal femoral head, it proved to have extremely poor wear characteristics, leading to build-up of high local concentrations of particulate wear debris. This wear debris provoked extreme adverse reactions in patients, leading to severe swelling and general discomfort.[5] Consequently, the use of PTFE for this purpose was abandoned.

Because of experiences of this type, there has been a shift in thinking and the

emphasis nowadays is on materials that will elicit a response from the body that is appropriate.[6] This may be, as in the case of titanium implants, anchorage without formation of fibrous capsule.[7] Although it desplays this desirable feature, titanium is by no means inert the human body. It may undergo corrosion,[8] and this can be so severe that the tissues close to the implant become darkened by the build up of titanium within the cells.[9] Despite the potential for such adverse effects, in general the presence of titanium is well tolerated by the body,[10] and the use of titanium for the fabrication of implants is a current feature of many branches of surgery.[11]

The successful use of biomaterials presents numerous challenges. A major one is the issue of maintenance, and in particular that most devices are implanted well into the body and therefore not freely available for inspection or repair. An artificial hip joint, for example, is completely inaccessible, except by major surgery, and hence cannot be routinely serviced. The body is a hostile environment, despite its sensitivity, and it provides very severe service conditions. In no other field of technology are manufactured items expected to function without maintenance for so long in comparably demanding conditions.

Life expectancy in the wealthier parts of the world is now of the order of 80 years, which means that many people now outlive the useful life of their own connective tissue.[12] This can be be quantified by considering what happens to the bones on ageing. In men, between the ages of 20 and 60, there is a 25% loss of cortical bone; in women, this loss is 35%.[13,14] These changes lead to losses in strength of the order of 80–90%,[15] and increases in the risk of bone fracture over the age of 50 of 13% in men and 40% in women.[16] As a consequence, by 80–90 years of age, 33% of women and 17% of men will have hip fractures.[17]

When synthetic materials are used to effect repairs, they must be able to survive for considerable lengths of time and without maintenance. However, it is rare to find an implant whose life expectancy exceeds 15 years, regardless of whether that implant is designed for orthopaedic, cardiovascular, dental or other application. This represents the major challenge in the field, and one that is extremely elusive. Despite much research activity in biomaterials science, the problem of maintenance-free durability remains with us, and there have been only marginal extensions in the anticipated lifetimes of implants as a result of considerable volumes of research in both materials and surgical techniques. On the other hand, what has been achieved is remarkable, and there is no doubt that biomaterials alleviate suffering and add to the quality of life for a very large number of individuals throughout the world.

2 Surgical Uses of Biomaterials

Typically, biomaterials are fabricated into a medical device of some sort, and employed in the body in this form. In this context, the term *device* has been defined by the United States Federal Drug and Food Administration (FDA) as '. . . any instrument, apparatus, implement, machine, contrivance, *in vitro* reagent or combination of these that is intended for diagnosis, prevention or

treatment of disease'.[18] This is a comprehensive definition, and includes those applications of synthetic materials in the human body where the material itself is simply placed, perhaps taking up the shape of a specially prepared cavity, as in dental filling materials or orthopaedic bone cements. Devices so defined are currently employed in a wide range of branches of surgery to treat a variety of conditions. Some of the more frequently employed examples of these are described in detail in the remaining sections of this chapter.

Orthopaedic Joint Replacement

As the body ages, it becomes susceptible to osteoarthritis, a condition in which the lubricating layer of cartilage covering the bone in joints degenerates.[19] This degeneration results in loss of freedom of movement of the joints, together with extreme pain. Both features contribute to the immobilisation of the patient, with potentially serious secondary effects on the health resulting from reduced exercise. The main joints that are affected are the hip and the knee, and treatment is by joint replacement, a procedure known as total joint arthroplasty. In this operation, the diseased joint is removed and replaced with one composed entirely of artificial materials. These maintain their location relative to the bone, and are required to survive preferably for the remaining lifetime of the patient.[20] Hip replacement is the most widely performed of the total joint arthroplasties, and an estimated 287 000 are performed each year throughout the world.[13]

The hip and knee, and also other joints, such as the shoulder, are complex and delicate structures. They comprise an optimised combination of articular cartilage, bone and synovial fluid.[21] Articular cartilage is a connective tissue that covers the bones, and is capable of bearing loads. It has a low coefficient of friction, thereby contributing to the natural lubrication of the joint.[22] Synovial fluid is a nutrient solution secreted within the joint,[11] which also partly exhibits a lubricating function. Human joints are prone to degenerative diseases, of which osteoarthritis (loss of articular cartilage) is the major one, but others also include rheumatoid arthritis (swelling of the synovial membrane) and chondromalacia (softening of the cartilage). Approximately 90% of the population over the age of 40 suffers to some extent from degenerative bone disease, a state of affairs which arises either because of excessive loading of the joints during the early life of the patient or because of failure of the normal repair processes later in life leading to degeneration. Such failure occurs by a mechanism or mechanisms which are not currently understood.

In total hip arthroplasty, the natural hip joint is replaced by an artificial one consisting of a femoral component that is usually a polished metal ball mounted on a metal stem, and an acetabular component that has a socket in which the ball sits and swivels as the patient walks. The femoral component is predominantly metal, either cobalt-chrome or a titanium alloy; the acetabular component, sometimes called a cup, is made from ultrahigh molecular weight polyethylene, UHMWPE. The use of a head smaller than that of the natural femur was one of the pioneering developments of Charnley. A small head

makes the pin easier to place and finish than a larger head, though the latter approach, using a head size equivalent to that of the natural femur, was used for some time in the so-called McKee–Farrar hip. The components of a Charnley-type hip are shown in Figure 1.1.

There are various designs of femoral pin and head in use. Stems vary in length, curvature and finish, and also in whether or not they have collars or other mechanical additions for spreading the load or integrating with the bone.

The components of the hip are generally held in place with a self-curing acrylic bone cement. This was originally based on the same material as denture bases, but has since undergone considerable study and modification. The cement is generally prepared by mixing methyl methacrylate monomer with pre-polymerised beads of poly(methyl methacrylate) that also contains a polymerisation initiatitor, typically benzoyl peroxide with dimethyl-*p*-toluidine as accelerator. On mixing, the monomer undergoes a rapid polymerisation and sets to yield a reasonably strong and rigid material within 10–20 minutes of mixing. The detailed chemistry of such bone cements is covered in Chapter 2. It has been claimed that the use of cement was the major factor in the success of this surgical technique, and prostheses of this type, cemented by poly(methyl methacrylate) have a success rate of 85–95% at 15 years.

Early hip replacements were often complicated because of a high incidence of infection. These problems were overcome by improvements in operating room procedures and the use of antibiotics following surgery.[23] There remain failures with the technique, of which the most common is so-called 'aseptic loosening', in which the femoral component of the joint becomes loose due to bone resorption around the cement. This has been assumed to be caused *inter alia* by individual patient intolerance of the poly(methyl methacrylate) bone cement and attempts have been made to overcome the problem by using a cementless surgical technique. This has often been accompanied by the use of specially prepared metal prostheses, with either roughened surfaces or with surfaces coated in plasma-sprayed hydroxyapatite.[24] Both of these surface-treatments are aimed at encouraging the growth of bone right up against the implant, a process known as *osseointegration*. Despite initially encouraging results, currently operations performed with cemented prostheses have superior outcomes, both in terms of patient mobility following the operation and survival rates of the implant.

A general problem with all artificial joints is that of stress transfer from synthetic materials, whose moduli are typically very different from that of bone.[25] In most cases, following the insertion of an artificial hip, the outer wall of the femoral cavity becomes more heavily loaded than in the natural hip, whereas the inner wall becomes more lightly loaded. Bone is a dynamic tissue whose form is maintained by a balance between the activities of the bone depositing cells (osteoblasts) and the bone resorbing cells (osteoclasts).[26] Bone is a piezoelectric material,[27] and thus responds when its pattern of loading changes. This alters the relationship between the activities of the osteoblasts and the osteoclasts. Following hip replacement, this change leads to the deposition of extra bone along the outer wall of the femur and the removal of

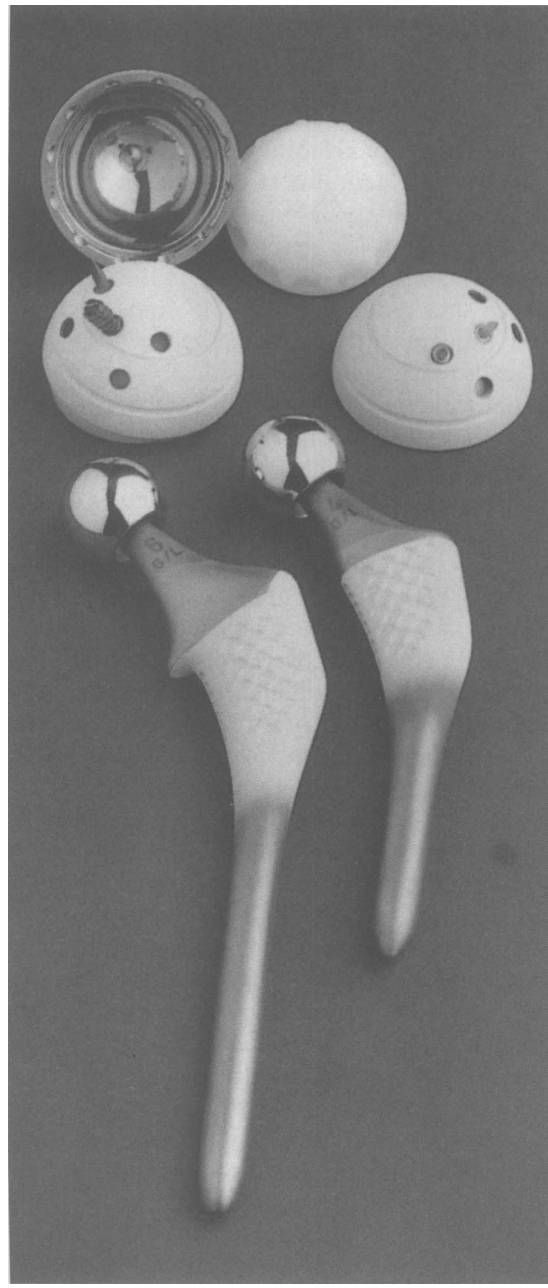

Figure 1.1 *Components of an artificial hip-joint for use without bone cement* (courtesy of Howmedica-Stryker Ltd)

bone from the inner wall. The inner wall is often described as experiencing 'stress shielding' and in extreme cases this can lead to the development of holes in the femoral wall, with disastrous effects on the overall strength of the replaced hip joint.

A final difficulty to be considered is that of wear of the acetabular cup by the artificial femoral head.[28] In recent years it has been realised that such wear is a major problem and it is currently receiving considerable attention from researchers. One approach to deal with it is to use ceramic femoral heads. Ceramics, typically alumina or, less commonly, zirconia, cause different wear behaviour of the UHMWPE acetabular cap than metals.[29] If a metal is scratched, it tends to creep in ductile fashion, lifting sharp edges along the length of the scratch, and these scrape out pieces of the polyethylene. By contrast, if a ceramic is scratched, because it is a brittle material, it tends to respond by losing material from its surface. This behaviour results in the retention of a smoother finish than the metal, and one which is still able to articulate with the polyethylene without scraping out debris. Because of these differences, ceramic heads cause considerably less damage to acetabular cups than metal ones, with correspondingly fewer problems of wear debris and adverse tissue response due to the accumulation of polymer particles in the region around the joint.[30]

After hips, the next most commonly replaced joint is the knee. Total knee replacement surgery was developed somewhat later than hip replacement, but since about 1974 has become a successful surgical technique. Knee replacement is required for similar reasons to hip replacement, most frequently degenerative loss of lubricating cartilage within the joint, leading to severe pain and progressive immobility. Replacement of the knee is more complicated than replacement of the hip, due to its more complex pattern of loading.[14] This arises partly from the concentration of force through the knee when an individual is standing, and partly because of the rotational motion of the tibia relative to the femur during walking.[31]

The components of the natural knee joint are illustrated in Figure 1.2. To replace this with an artificial joint requires a number of features.[32] The articulating end of the femur needs to be replaced by a lightweight component that typically consists of a thin, rigid shell with an attached fixation system to anchor the device to the bone. Details of the construction vary from device to device, and may include a shaft to stabilise the component relative to the femur. Metals, either a cobalt-chrome or a titanium alloy, are used to fabricate this component, since they combine the necessary properties of high strength, high modulus and low wear rate. This component is either cemented in place with a poly(methyl methacrylate) bone cement, or finished in such a way that full osseointegration can occur readily.

To replace the tibial aspect of the joint, a relatively broad platform is inserted. This typically consists of a stiff metal tray, with a polymeric component, usually made from UHMWPE, providing the articulating surface. This UHMWPE component is subject to very high loading as the patient walks, and this leads, on occasion, to failures due to creep or fatigue. As with

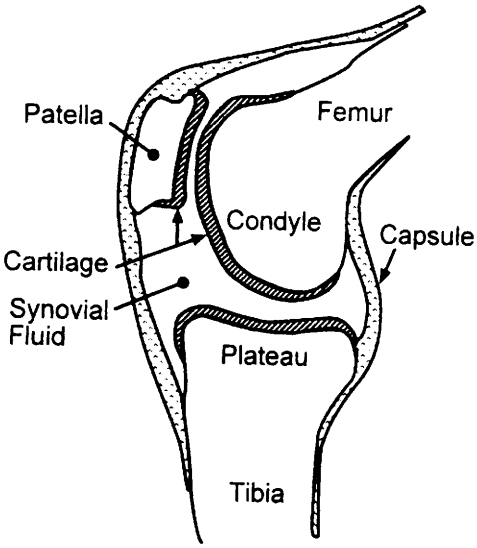

Figure 1.2 *Diagram of the natural knee joint*

hip joints, the UHMWPE can experience significant wear due to the repeated motion of the metallic component in contact with it.[23] The topic of wear of UHMWPE and its biological effects is dealt with in Chapter 2.

The bone into which these replacement joints is placed has a complex structure. It consists of hydroxyapatite together with the fibrous protein collagen and water, as well as minor components, some of which are critical for bone to perform its biological function. The mineralised tissue of vertebrates is different from that of other living groups in that it represents a more extensive component of their bodies and also that the mineral phase is a form of calcium phosphate, rather than calcium carbonate or silica.[33]

There have been numerous studies of the mechanical properties of bone, but the results are difficult to interpret. This is because bone not only behaves like all materials in giving different values of strength depending on loading regime, *e.g.* whether in tension, compression or flexion and on rate of loading, but also it is anisotropic, *i.e.* its properties are not the same in all directions.[28] Properties also change with age and with the health of the individual.[34] For example, in a study of the human femur, the tensile strength was found to vary from about 120 MPa at age 20 to 65 MPa at age 95.[35] Similarly ultimate tensile strain went down from 3.5% to about 1% over the same age range. By contrast the tibia showed much less change.[36]

The organisation of bone varies with bone type. Broadly speaking, the structure involves the interaction of the two solid phases, collagen and hydroxyapatite. Hydroxyapatite crystals occupy gaps between the collagen fibres[37] and are bonded to the collagen through interactions of the polar groups on the protein molecules with the calcium phosphate crystal structure.[38] The organisation of the collagen varies between the types of bone. In

woven bone, which is laid down rapidly, typically in the foetus or in the callus that forms during the repair of fractures,[28] the collagen fibres show little orientation. In lamellar bone, the collagen is more ordered, with collagen fibrils in individual lamellae being lined up in more or less the same direction, but at right angles to the fibrils in the immediately adjacent lamellae.[39] Parallel-fibred bone also occurs, and in this the collagen fibrils are all aligned with the long axis of the bone.[40]

Tendons and Ligaments

Tendons and ligaments are tough, collagenous tissues with connective functions. Tendons connect bone to muscle, while ligaments connect bone (or cartilage) to bone. They are flexible and capable of contraction, and because of these properties, are able to move the bone or cartilage to which they are attached.

There are at least twelve different types of collagen found in nature, of which types I, II and III predominate in mammalian tissues.[26] These types form the structural fibres in tendon and also skin, cartilage and cardiovascular tissue. They are triple-helical molecules, mainly based on the amino acids glycine, proline and hydroxyproline. Tendon also contains type V collagen, whereas ligament is made up of type IV collagen.[26]

Tendon and ligament damage is most often sustained through injury to athletes engaged in contact sports, but may also occur in military personnel, labourers and factory workers. In cases of sports injuries, transplanting of autogenous tissue has been a successful technique for restoring normal joint function, for example of the knee.[41,42] The problem with this approach is that recovery time following surgery is prolonged. Alternatively, where a tendon or ligament is damaged but not completely torn, immobilisation of the joint leads to healing with the formation of scar tissue. This is also not completely satisfactory, because scar tissue is inferior biomechanically to undamaged tendon or ligament; it is weaker and less readily contracted.[43]

The most frequently damaged ligament is the anterior cruciate ligament of the knee.[14] Injury to this ligament is increasing, due to the increase in athletic activity in many countries, notably the United States. Replacement of this ligament is not straightforward and no medical devices employing synthetic materials have yet been approved by the United States Food and Drugs Administration for this purpose. Because of this, biological graft material is often used as a substitute for the natural ligament. However, various synthetic materials have been studied experimentally and a number of devices have received conditional approval for clinical use. These include carbon fibres, poly(ethylene terephthalate), polytetrafluoroethylene and braided polyethylene.[14] Composite structures, such as carbon fibre coated with poly(lactic acid), have also been examined,[44] though concern has been expressed about the fate of carbon particles generated in use once the poly(lactic acid) has degraded.[14]

There have also been problems reported with the morphology of the collagen induced in the region of artificial ligament materials.[45] Synthetic