CHAPTER 1

Synthetic Materials in Medicine

1.1 Introduction

The use of synthetic materials in the body by medical and dental surgeons to repair the body and restore function has grown considerably in the last 50 years. However, the concept of using artificial materials to repair the body is very old. 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] This surgical repair technique, known as total hip arthroplasty, has grown spectacularly, and since Charnley's original cemented hip replacements there have been a variety of new materials and new designs for implantable devices. These are now available not only for hips, but also for knees, toes and fingers.

Artificial materials used in the body in this way are called *biomaterials.* This use of the term appears to originate in 1967 with the first 'International Biomaterials Symposium' at Clemson University, South Carolina, since when it has been used extensively in this way. In many ways, to apply the word *biomaterials* to synthetic materials is not very satisfactory because, by analogy with 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.*[2] 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 organization which ran the meeting, the European Society for Biomaterials, because the Society's objective from the time it was established in 1976 was to promote the study of

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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 stay in the body for some considerable time. Materials used for devices used only in surgery, such as sensors or catheters, are not usually regarded as biomaterials. They may interact with the body, but this 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 used in various novel ways in medicine, for example as temporary scaffolds and supports for bone immobilization. These enable the body's own repair mechanisms time to bring about complete healing without premature loading and potential failure. Under these circumstances, the polymers become biomaterials, because they must interact with the body for a considerable time.

The field of biomaterials science involves 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*.[2] As stated in this definition, biocompatibility is not a property of a material as such. Instead, 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 in contact with blood, for example 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 desirable, but nowadays inertness is not thought possible. Even materials that seem inert in most technical applications, such as polytetrafluoroethylene (PTFE), turn out to be highly active when placed within the body. PTFE was once used to fabricate the acetabular cups used in experimental hip replacement surgery.[3] When used in conjunction with a metal femoral head, it was found 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.[2] In the case of titanium implants, this may be that there is no formation of fibrous capsule.[4] Although it displays this desirable feature, titanium is not inert in the human body. It can corrode,[5] yet the presence of titanium is well tolerated by the body,[6] and the use of titanium for implants is found in many branches of surgery.[7]

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 cannot be easily inspected or repaired. An artificial hip joint, for example, is completely inaccessible, except by major surgery, and so cannot be routinely serviced. The body is a hostile environment, despite its sensitivity, and the resulting service conditions are severe. Nowhere else in technology are manufactured items expected to function without maintenance for so long in such demanding conditions.

Life expectancy in the wealthier parts of the world is now around 80 years, which means that many people now outlive the useful life of their own connective tissue.[8] As people age, so there is a loss of cortical bone, resulting in substantial reductions in bone strength. This means that specific fractures, such as of the hip, become common in the elderly.[9]

When synthetic materials are used for repairs, they must be able to survive for considerable lengths of time 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 large amounts of research in the field of biomaterials science, the problem of maintenance-free durability remains with us. There have been only marginal extensions in the anticipated lifetimes of implants as a result of our increased knowledge of 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 people throughout the world.

1.2 Surgical Uses of Biomaterials

Biomaterials are usually made into a medical device of some sort, and employed in the body in this form. 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'.[10] This is a comprehensive definition, and includes those instances where the material itself is simply placed and takes up the shape of a prepared cavity or space, as in dental filling materials or orthopaedic bone cements. Devices defined in this way are currently used in various branches of surgery to treat different conditions. Some examples are described in detail in this chapter.

1.2.1 Orthopaedic Joint Replacement

As the body ages, it may develop osteoarthritis. This is where the lubricating layer of cartilage covering the bone in joints degenerates.[11] When this occurs, the joints lose freedom of movement and the patient experiences pain. Both features make the patient immobile and there may be serious secondary effects on the health because the patient is less able to exercise. The main joints affected are the hip and the knee, and surgical treatment is by joint replacement, a procedure known as total joint arthroplasty. In this operation, the diseased joint is removed and replaced with one made completely from artificial materials. Having been placed in the body, they are required to survive for as long as possible, preferably for the rest of the patient's life.[2] Hip replacement is the most widely performed of the total joint arthroplasties, but there are also a very large number of knee replacements performed each year.[2]

The hip and knee, and also other joints, such as the shoulder, are complex and delicate structures. They consist of a combination of bone, articular cartilage and synovial fluid.[12] Articular cartilage is a connective tissue that covers the bones, and is able to bear loads. It has a low coefficient of friction, and this contributes to the natural lubrication of the joint.[13] Synovial fluid is a nutrient solution secreted within the joint,[14] which also has a partial 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. This arises either because of excessive loading of the joints during the early life of the patient or because the normal repair processes fail to an extent later in life leading to degeneration.

In total hip arthroplasty, an artificial hip is placed in the body.[15] It consists 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 mainly 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 by Charnley. A small head makes the pin easier to place and finish than a larger head, although 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 they have collars or other mechanical additions for spreading the load or integrating with the bone.

The components of the hip are often held in place with a self-curing acrylic bone cement.[16] This was originally based on the same material as denture

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

bases, but has since undergone considerable study and modification. The cement is generally prepared by mixing methyl methacrylate monomer with pre-polymerized beads of poly(methyl methacrylate) that also contains a polymerization initiator, typically benzoyl peroxide with dimethyl-*p*-toluidine as accelerator. On mixing, the monomer undergoes polymerization 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.[16]

Early hip replacements often failed because of a high incidence of infection. These problems were overcome by improvements in operating room procedures and the use of antibiotics following surgery.[17] There are still some failures with this technique, the most common of which is so-called 'aseptic loosening', in which the femoral component of the joint becomes loose due to bone resorption around the cement.[18] This has been assumed to be caused partly 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.[19] 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 better 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 very different from that of bone.[20] 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).[21] Bone is a piezoelectric material,[22] and so it responds when the loading pattern 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 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 serious effects on the strength of the replacement hip joint.

Another difficulty is that of wear of the acetabular cup by the artificial femoral head.[23] In recent years it has been realized that this sort of wear is a major problem. One approach to deal with it is to use ceramic femoral heads. These tend to cause less wear than metal surfaces articulating with the polymer and therefore they generate less wear debris. This, in turn, reduces the occurrence of adverse biological effects, including bone resorption.[24]

Knee replacement is also common in modern orthopaedic surgery. Total knee replacement surgery was developed later than hip replacement, and since about 1974 has become a successful surgical technique.[25] Knee replacement is required for similar reasons to hip replacement, specifically degenerative loss of lubricating cartilage within the joint, leading to severe pain and gradual immobility. Replacement of the knee is more complicated than replacement of the hip due to its more complex loading pattern. This is partly because of the concentration of force through the knee when an individual is standing, and also because of the rotational motion of the tibia during walking.[26]

The components of the natural knee joint are illustrated in Figure 1.2. To replace this with an artificial joint requires several things.[27] The articulating end of the femur needs to be replaced by a lightweight component, typically a thin, rigid shell with an attached fixation system to hold the device in place in the bone. Details of the construction vary from device to device, and may include a shaft to stabilize the component in the femur. Metals, either a cobalt–chrome or a titanium alloy, are used to manufacture this component, because 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 a way that encourages full osseointegration.

To replace the tibial aspect of the joint, a relatively broad platform is inserted. This consists of a stiff metal tray, with a polymer component, usually

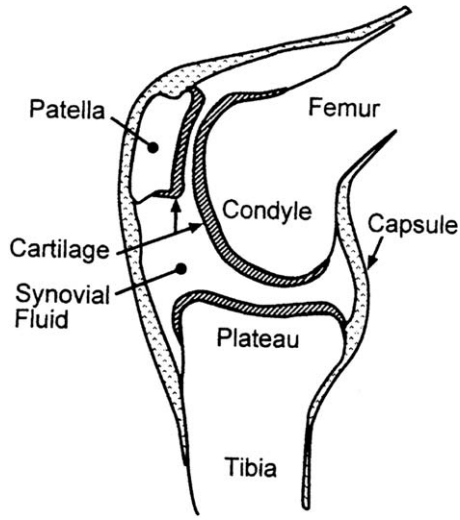

Figure 1.2 Diagram of the natural knee joint.

made from UHMWPE, to provide the articulating surface. This UHMWPE component is subject to very high loads as the patient walks, which may cause failures due to creep or fatigue. As with hip joints, the UHMWPE can undergo significant wear due to the repeated motion of the metallic component in contact with it. The topic of wear of UHMWPE and its biological effects is dealt with in detail in Chapter 2.

The bone that supports a replacement joint 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 mineralized tissue of vertebrates is different from that of other living groups in that it makes up a greater proportion of their bodies and also that the mineral phase is a form of calcium phosphate, rather than calcium carbonate or silica.[28]

The mechanical properties of bone have been widely studied, 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.[29] Properties also change with age and with the health of the individual.[30] For example, in a study of the human femur, the tensile strength was found to drop from about 120 MPa at age 20 to 65 MPa at age 95.[31] Similarly, ultimate tensile strain went down from 3.5% to about 1% over the same age range.

The organization of bone varies with bone type. In all cases, the structure involves the interaction of the two solid phases, collagen and hydroxyapatite. Hydroxyapatite crystals occupy gaps between the collagen fibres[32] and are bonded to the collagen through interactions of the polar groups on the protein molecules with the calcium phosphate crystal structure.[33] The organization of

the collagen differs 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, 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.[34] Parallel-fibred bone also occurs, and in this the collagen fibrils are all aligned with the long axis of the bone.[35]

1.2.2 Tendons and Ligaments

Tendons and ligaments are tough tissues with connective functions made up of the protein collagen. 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 12 different types of collagen found in nature, of which types I, II and III predominate in mammals.[36] 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.[36]

Damage to tendons and ligaments is most often sustained through injury to athletes engaged in contact sports. However, it may also occur in military personnel, labourers and factory workers. In the case of sports injuries, transplanting of autogenous tissue has been a successful technique for restoring normal joint function, for example of the knee.[37] The problem with this approach is that it takes a long time to recover after surgery. Alternatively, where a tendon or ligament is damaged but not completely torn, immobilization of the joint causes healing to occur with the formation of scar tissue. This is unsatisfactory, because scar tissue is inferior biomechanically to undamaged tendon or ligament; it is weaker and less readily contracted.[38]

The most frequently damaged ligament is the anterior cruciate ligament of the knee.[39] Injury to this ligament is occurring more and more 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 made from synthetic materials have yet been approved by the United States FDA 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, polyethylene terephthalate, polytetrafluoroethylene and braided polyethylene, as well as composite structures involving these materials.[39]

Synthetic polymers, such as UHMWPE, have inadequate fatigue properties for use as replacements for the anterior cruciate ligament and hence they do not make acceptable permanent substitutes for ligaments. Instead, this type

of synthetic material should only be used for the fabrication of temporary (degradable) scaffolds.[40] Acceptable polymers for this use are poly(glycolic) or poly(lactic acid), or related copolymers, and they degrade in the body over time periods ranging from a few weeks to several months, depending on their composition. To date, these materials have been mainly studied experimentally using animal models, and it is early days in the use of these materials for surgical repairs in human patients.

1.2.3 Cardiovascular Implants

Diseases of the cardiovascular system contribute to approximately 40% of the deaths of people within the EU.[41] A major cause of death is the condition known as atherosclerosis, which affects large- and medium-diameter blood vessels, especially the aorta, coronary arteries and cerebral arteries. In this condition, fatty deposits and fibrous tissue partly formed from collagen precipitate onto the internal wall of the blood vessel, narrowing the diameter. This leads to abnormal dilations of the affected blood vessels known as aneurysms. They can go on to cause tearing or bursting of the vessel walls, which results in the death of the patient.[42]

Another possible defect of the cardiovascular system is leaky heart valves, which like atherosclerosis become more common as individuals become older. Both atherosclerotic blood vessels and leaky heart valves are now routinely replaced, either with synthetic or natural materials. Examples of materials that have been used are given in Table 1.1.

An important disease of the cardiovascular system is failure of the natural heart valves, where they fail to close properly during the heart beat and therefore leak.[43] These damaged valves can be replaced with prosthetic devices. Heart valve replacement has used two approaches, either mechanical devices consisting of a disc or ball in a metal framework, or bioprosthetic valves, made from bovine or porcine tissue. The mechanical device is more common, and is used in about 75% of all heart replacement cases.[43] Neither type is totally satisfactory, and each may have problems in service. The synthetic heart valve requires patients to remain on anticoagulant medication for the rest of their lives to prevent clotting of the blood in the region of the implanted material. On the other hand, although patients receiving bioprosthetic valves do not require permanent anticoagulant treatment, these valves may undergo calcification or degeneration.

In the course of their use, all cardiovascular prostheses must come into contact with blood. Ensuring that blood responds appropriately to the

Table 1.1 Materials used in cardiovascular surgery.

Size	Material
12–38 mm diameter	Polyethylene terephthalate (PTFE)
5–10 mm diameter	Polyethylene terephthalate (PTFE)
<4 mm diameter	Autografts

Table 1.2 The composition of blood.

Substance	Vol%	Comments
Water	35	
Proteins		
Albumin	1–2	Molar mass 69 000
Fibrinogen	0.2	Molar mass 34 000
Ions	<0.5	Molar mass <100
Cells		
Red blood cells	45	Biconcave disc, 8 μm×1–3 μm thick
White blood cells	<1	Spherical, 7–22 μm diameter
Platelets	<1	Disc, 2–4 μm diameter

presence of foreign bodies is a major challenge. Blood is very prone to clot,[44] and this must be prevented around implanted devices. When devices and materials fail to provoke clotting, they are described as haemocompatible. One approach to enhance the haemocompatibility of polymeric materials in particular has been to change the hydrophobic/hydrophilic balance of the surface. Extremes of either highly hydrophilic or highly hydrophobic character give the best results for haemocompatibility, whereas a surface somewhere between the extremes tends to provoke clotting.[45]

The composition of blood is shown in Table 1.2.

The coagulation of blood (clotting) occurs easily, and this is desirable because it defends the body against excessive blood loss when there are small leaks in the cardiovascular system. Clotting is a complex process,[44] and may be initiated either *via* the surface, the so-called intrinsic cascade, or *via* tissue damage, the extrinsic cascade. These lead to the formation of complexes between the blood proteins and the platelet surfaces, followed by activation of prothrombin to form thrombin and fibrinogen to form a fibrin clot. Coagulation of the blood can also trigger the kinin system, which results in leakage of fluid from the vascular system into the surrounding tissues, a process that results in inflammation. Synthetic materials can interact with various stages of the coagulation pathway, thereby provoking thrombus formation. They can also cause prolonged inflammation, which may compromise implant function and cause a variety of unacceptable side effects.[2]

The initial interaction between the body and a synthetic material may be influenced by several factors, including composition, surface energy, roughness and topography.[46] When a material is implanted into the cardiovascular system, a cascade of events follows.[47] This cascade begins with water molecules arriving at the implantation site, where they hydrogen bond *via* hydrogen or oxygen atoms. Ions become incorporated into this water layer, and these are followed by the arrival of proteins, which interact with them and with the water molecules to become associated with the layer. Gradually, there is a build-up of biomolecules in this layer, the precise details of which vary depending on the implanted material. However, the nature of the proteins and other biomolecules deposited determines which serum components present in the extracellular fluid actually become

adsorbed on the surface. The most common substances adsorbed are fibrinogen, gamma-globulin and albumin, but other substances may also be deposited. The amounts deposited are related to their concentration in the extracellular fluid. Once this plasma protein layer has been adsorbed, a cross-linked fibrin network can develop. If fibrin formation is too rapid, a thrombus may develop. On the other hand, if it occurs slowly, the process of fibrinolysis may be activated and thrombus formation prevented.[47]

Overall, the goal of developing biomaterials that show full haemocompatibility is probably the toughest challenge facing scientists in this field. The sensitivity of the blood towards coagulation, and the ease with which foreign materials trigger the process, means that implanting devices into the cardiovascular system is always difficult. Although good progress has been made, as evidenced by the widespread use of items such as synthetic heart valves and other devices, there remains a long way to go, and the ideal of a synthetic material that can be implanted without the patient needing to be placed on permanent anticoagulant therapy is still to be realized.

1.2.4 Ophthalmic Implants

Synthetic materials are used to improve and maintain vision, a requirement of growing importance as the population continues to age. The eye itself is a complex organ that is held within the bony orbit of the skull by extrinsic eye muscles. The structure of the eyeball is shown in Figure 1.3.

The eyeball is about 2.5 cm in diameter. It is made up of three layers: the fibrous outer coat, the vascular middle layer and the light-sensitive inner lining. In the back of the eye is a thin, pigmented membrane called the choroid which supports the retina. The retina is a light-sensitive part of the eye which functions by converting light intensity and colour into electrical

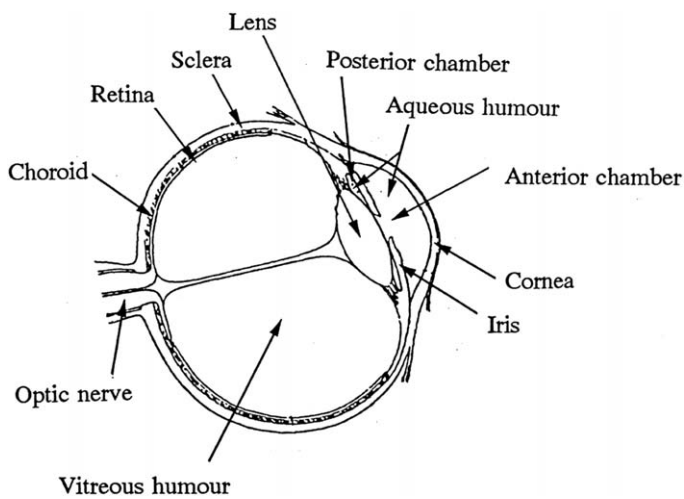

Figure 1.3 Structure of the eyeball.

signals for transmission to the brain *via* the optic nerve. As well as its pigmented epithelium, the retina contains cells known as rods and cones. The rods are sensitive to dull light and are essentially responsible for the perception of movement and shape. The cones are sensitive to bright light and are responsible for the perception of colour and sharp outline.

The eyeball is filled with fluid. The main part, behind the lens, is filled with the vitreous humour, a viscous, gel-like liquid containing thin collagen fibrils. The liquid itself is a solution of hyaluronic acid, which is a linear polymer of D-glucaronic acid and *N*-acetylglucosamine. The molar mass is highly polydisperse, and ranges from 77 000 to in excess of 100 000.[48] In front of the lens is a chamber containing the aqueous humour, which, as its name suggests, is a low-viscosity liquid. It is maintained at a pressure of about 24 mmHg by a balance between continual production and drainage of the fluid.

The lens is formed from collagen, cell attachment factors and proteoglycans characteristic of the lens tissue. It also contains an unusual class of protein called crystallins that are arranged in such a way that they are transparent.[49] A common problem in older patients is loss of transparency in the lens leading to cataract formation. This in turn results in loss of vision.

Treatment of cataracts is now routinely achieved by the implantation of synthetic intraocular lenses. These lenses consist of an optical portion through which light passes, and a loop portion for anchoring the lens within the eye.[50] The optical portion is typically made from poly(methyl methacrylate), or PMMA, which has excellent clarity and is very biocompatible when implanted into the eye. However, other materials have also been used, as shown in Table 1.3.

Usually, intraocular lenses are placed in the posterior chamber of the eyeball, although anterior chamber placement is also used occasionally. The anterior chamber tends to be used if the eyeball has been severely damaged, for example when the posterior chamber has been ruptured and there has been loss of the vitreous humour.[51] Posterior chamber placement is achieved by removal of the natural opaque lens and insertion of the synthetic lens into the vacant capsular bag. This is not straightforward, and a major difficulty with the use of intraocular lenses is ensuring that they are adequately fixed for long-term service.[52]

Although PMMA is the material most widely used for lenses, other polymers have been used, notably silicones. These have the advantage of being flexible, so can be folded for insertion through incisions. This causes less damage to the endothelium than the placement of PMMA lenses, a feature that may be important in certain patients.[53]

Table 1.3 Materials used in intraocular lenses.

Component	Material
Optical portion	PMMA, poly(2-hydroxyethyl methacrylate), silicone
Stabilizers	Antioxidants, UV absorbers
Anchor	Metals, nylon, glass, polyimide, polyethylene

Table 1.4 Materials used for rigid gas-permeable contact lenses.

Polymer	Comments
Acrylate with microscopic holes	Increased permeability
Fluorinated methacrylate or pyrolidone	Reduced corneal swelling for up to 60 days
Silicones	Hydrophobic, hence interact with insoluble
Silicone-methacrylates	Not permeable enough for extended wear

Polymers are also used to make contact lenses as an alternative to spectacles for the correction of defective vision. As with intraocular lenses, PMMA is widely used for this purpose. The drawback is that it is rigid and also has a low oxygen permeability, both of which are disadvantages in this application. Making sure there is an adequate supply of oxygen to the cornea is vital for the health of the eyeball, and because of this, contact lenses with higher rates of oxygen diffusion have been developed.[54,55]

Initially, soft contact lenses were developed because diffusion coefficients for oxygen are higher through these gels than through rigid polymers. However, soft contact lenses become less permeable to oxygen as they age. They are also susceptible to deposition of lipomucoprotein from the tear film and to growth of fungi and bacteria. For this reason, rigid gas-permeable materials have been developed,[56] examples of which are listed in Table 1.4.

Despite these developments, it is still difficult to find a material suitable for extended wear. Unless lenses are removed at least for periods of sleep, and preferably at other times, complications may arise. These include corneal abrasions, hypersensitive reactions, hypoxia, infections and toxicity.[57] Research is still underway to try to solve the problem of extended wear of contact lenses, and there is little doubt that, if successful, such lenses would prove popular.

Defects in vision may occur not only because of problems with the lens. There is also the problem of glaucoma. This is a condition in which the pressure of the intraocular fluid becomes elevated, leading to progressive damage to the optic nerve, with resulting loss of vision. The main surgical treatment is to insert an opening that allows fluid to drain through the sclera/cornea into the subconjunctival space. For some patients, it is advantageous to place a drainage implant at this site to facilitate the process.[58] Typical devices have drainage tubes made of silicone and with plates fabricated from various polymers, including silicone and PMMA.[59]

Finally, there are a number of other uses for synthetic materials in ophthalmology other than for the lens or glaucoma drainage. These include artificial tear solutions for patients with dry-eye conditions.[60] Such solutions typically contain a variety of substances, such as carboxymethylcellulose and sodium hyaluronate, although formulations vary, and there is no ideal formulation to suit the majority of patients who suffer from dry-eye syndrome.[60]

1.2.5 Dentistry

The structure of a typical tooth is shown in Figure 1.4. The destruction of its fabric is a disease called dental caries, which, although preventable,

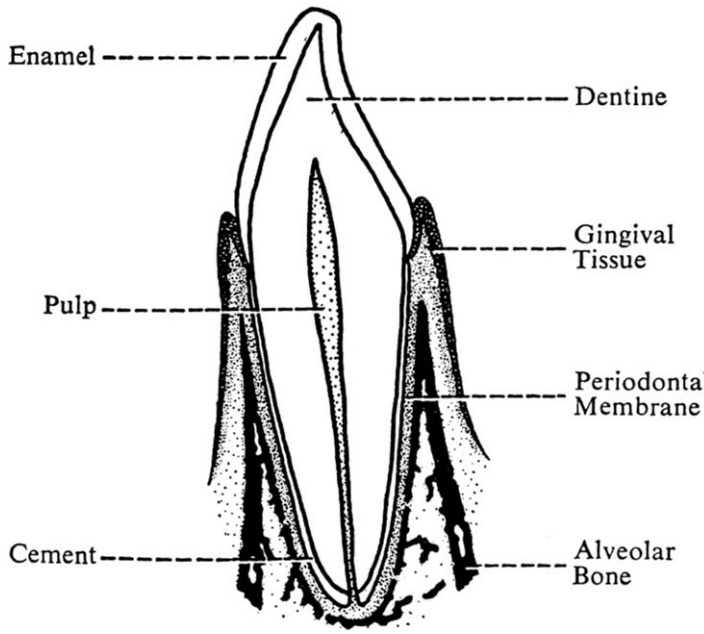

Figure 1.4 Structure of a tooth (incisor).

is one of the most widespread diseases of civilization.[61] Dental caries occurs when there is attack on both the enamel and the dentine of the tooth by acids. These acids are generated as the result of metabolic activity of bacteria within the plaque that accumulates on the tooth surface. The main acid that is formed is lactic acid, but acetic acid is also generated in smaller amounts by active caries.[62] Initial attack is quite localized on the surface of the enamel, but as it penetrates the softer dentine, it tends to balloon out and undermine the surface layer of enamel.

Diet contributes to dental decay, especially the presence of refined sugar. Sugars are the food source for bacteria in the plaque, and are metabolized to generate the acids that cause the damage. The pH of the mouth drops rapidly after the intake of sugar, as was first demonstrated by Stephan in his classic study.[63] He gave his subjects a mouth rinse of glucose solution, then measured the pH at the surface of the tooth over the next hour. His findings are shown in Figure 1.5.

The critical factor in caries development is the time for which the pH stays below 5.5. Stephan's results showed that in patients who already had a significant amount of tooth decay, the pH stayed below this critical value for longer than it did in those without decay.

Sucrose is metabolized to form intracellular and extracellular polysaccharides. These sugars enable the bacteria to cling on tenaciously to the tooth surface, and provide a source of energy for continued metabolic activity. The

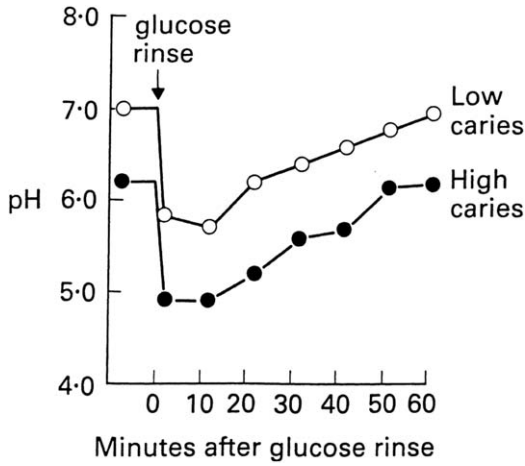

Figure 1.5 Curve of pH *vs* time following administration of a glucose drink. Reproduced from ref. 63 with permission from Elsevier, Copyright 1940.

main species responsible for caries is *Streptococcus mutans*, although other bacteria are also involved.

Tooth decay is a particular problem among the young, who tend to consume sweets, and also among the elderly, who often suffer from dry-mouth syndrome as a side effect of medication, and so resort to consuming sweet drinks and to sucking boiled sweets to relieve the discomfort. These days, these patients are likely to have at least some of their natural teeth, and they are susceptible to attack by caries that occurs as a result of the increase in sugar consumption.

Decayed teeth are repaired by cutting out the carious tissue, usually with a drill. The tooth is then repaired with an appropriate restorative. For many years, the most widely used and cost-effective material has been silver amalgam, although now there are environmental concerns with this material and its use is due to be phased out over the next few years.[64] In its place, there are tooth-coloured alternatives based on polymers. These are generally bonded to the tooth using either the inherent adhesive nature of the restorative, or special bonding agents.[65]

Tooth loss, which may result from severe caries or from periodontal disease in middle life, has conventionally been treated by providing dentures. These may be either full or partial, depending on the severity of the loss. More recently, partial tooth loss has been treated with the use of implants.[66]

Dental implants have mainly been used as replacements for tooth roots or tooth root analogues. They have also been used successfully to facilitate orthodontic tooth movement and also for prosthetic treatment of craniofacial defects. In selecting a patient for implant treatment, specific biochemical and biomechanical requirements have to be taken into account. For example, there should be no disease that would compromise wound healing. Conditions such as diabetes, osteoporosis and various

cardiovascular diseases may rule out implants. In general, patients should be in good health, be psychologically stable and have adequate bone density at the site of the proposed implant. Dental health should be good and especially healthy oral tissues are required.

The main material used for dental implants is titanium and its alloys. These are used because of their excellent bone biocompatibility and their ability to osseintegrate.[67] To replace teeth, titanium support structures are implanted into the jaw and used to support ceramic teeth which look life-like in the mouth.

As well as titanium-based implants, other materials have been used in dental implantology. For example, particles of synthetic hydroxyapatite have been used to improve healing in patients who have had periodontal surgery.[68] When used in this way, the hydroxyapatite becomes surrounded by collagen early in the healing process, and is gradually resorbed as natural bone is deposited. Synthetic hydroxyapatite of this type may also be used to augment the alveolar ridge in edentulous (*i.e.* toothless) patients, and in this way provide improved support for dentures. Similarly, bioactive glass carried in inert oils may be used to provide bone repair in this way.[69,70]

1.2.6 Wound Dressings and Artificial Skin

Wounds to the skin in the form of minor cuts and abrasions are common occurrences and usually need nothing more than to be kept clean and dry. For more extensive skin damage, for example severe burns, synthetic materials are used, either in the form of sterile dressings or as artificial skin. These limit the entrance of foreign matter into the skin and also prevent loss of fluid and heat from the surface of the skin.

In a typical person, the skin occupies an area of approximately 2 m^2. Skin tissue has a variety of functions, including regulation of body temperature, wound repair, protection from disease and removal of waste.[71] It also serves to protect the body's internal organs from injury.

The skin is divided into two distinct regions: the outer part, called the epidermis, and the inner part, called the dermis.[72] The epidermis varies in thickness, depending on its location, and is thickest where the skin needs to bear the highest loads, *i.e.* on the palms of the hands and the soles of the feet. The very surface layer of the epidermis consists of the stratum corneum, a layer consisting of dead cells that are continually lost by attrition and replaced in a dynamic process as the cells arise in the dermis and grow outwards.

Wound dressings and artificial skin are used to repair skin damage caused by bed sores, burns, cancer excision and complications of conditions such as diabetes (diabetic skin ulcers) and insufficient output from the heart (venous statis skin ulcers). Of these, bed sores are becoming more frequent. This is because of the increased numbers of patients living well into old age, but becoming progressively bedridden or seriously ill for extended periods of time. Bed sores, known as pressure sores or decubitis ulcers, have a number

of causes, including reduction in capillary blood flow to the skin, infection and lack of sensation in the skin.[73] Skin ulcers of this type commonly occur at various points in the lower half of the body, including the hips, buttocks, knees, ankles and heels. Bacterial contamination may occur, complicating the treatment of the original condition. These ulcers can be treated in a number of ways, including cold compresses, barrier dressings and disinfectant washes.

Ulcers may occur with diabetes or cardiac dysfunction and arise because of circulatory problems. In diabetes, a result of the presence of excess glucose in the blood is the formation of a glycated derivative of collagen in the blood vessel walls. This leads to thickening of these walls, with resulting premature arteriosclerosis. This, in turn, causes skin ulcers to form, and they usually prove difficult to heal. A variety of dressings have been used for treating these ulcers, many of which are of biological origin, typically collagen sponges and other reconstituted collagen products.

In the case of severe burns, a variety of wound treatments have been developed that are based on synthetic polymer materials. Re-establishment of a sound natural skin needs the skin to be kept wet, and dressings are designed to maintain moisture within the wound.[74] In addition, they are flexible to cover the wound surface completely and are also antiseptic and haemostatic.[75]

Polymers that have been used in wound dressings for burns are listed in Table 1.5.

Tissue engineering has been employed to make a variety of constructs for the treatment of skin damaged by burns and other serious wounds.[76] Such tissue-engineered skin is based on a combination of natural and artificial materials, and involves cells being supported on an appropriate scaffold.[77] Constructs of this type have been used with some success over the past 20 years or so, and they show considerable promise. However, there are problems. The major one is that they lack vascularization,[76] although there is a large amount of research currently underway aimed at improving this and developing constructs that can vascularize quickly.[77] This would allow the artificial skin to become fully functional skin in the shortest possible time.

Other problems with tissue-engineered skin is that it tends to lack flexibility, certainly compared with natural skin.[76] These constructs tend to be expensive and to have short shelf-lives.[78] As a result of these drawbacks, the extent to which these constructs have been used routinely has been limited.[76] Nonetheless, they are promising, and given the amount of interest

Table 1.5 Synthetic polymers used in wound dressings.

Polyurethane (used with adhesive)
Composite films of polyurethane with carboxymethylcellulose or polyethylene
Poly(2-hydroxyethylmethacrylate)
Polyurethane grafted with acrylamide
Silicone membrane on nylon velour
Poly(ethylene oxide) bonded to polyethylene mesh

they are attracting, there is every likelihood that the disadvantages will be overcome, and tissue-engineered full skin replacements will become available to wider groups of patients.

Because of these difficulties, skin grafting continues to be widely used for burns victims. This is despite the fragility of the grafts and other problems with the technique. Future developments in this area, though, are likely to be based on tissue-engineered devices, and to involve at least some use of biomaterials in the treatment.

1.2.7 Facial Implants

Facial deformity may be caused by congenital disorders, severe trauma or the surgical removal of tumours, and it may involve the jaws, skull or face.[79] Congenital disorders include cleft lip and palate, and microtic ear. Microtic ear is the malformation of the external part of the ear, so that only a small flap or significantly misshapen structure is present. It usually occurs asymmetrically, *i.e.* only one ear is affected.

Cleft lip and palate are dealt with surgically, with the clefts being stitched or repaired, sometimes with autografts. Other deformities make use of synthetic materials. For example, microtic ears can be replaced by silicone prostheses supported on partially implanted abutments. The ear is typically modelled from the normal ear of the patient and is mounted on a metal support, made from a titanium alloy. These implants require careful management, because they penetrate the skin. They should be kept scrupulously clean by the patient, preferably with the aid of a bactericidal soap. Antifungal and antibacterial creams may also need to be applied.

In the case of severe trauma, it may be necessary to place an implant-stabilized facial prosthesis that needs to contain a false eye. The basic principles of preparing these prostheses are similar to those for a replacement ear. The titanium alloy needs enough bone density to become firmly anchored, and the implant must be kept clean. The major part of the prosthesis is mounted on a metal piece or pieces, which clip onto the implant for retention.

Facial prostheses of this kind must be monitored carefully. The colour must be stable, but exposure to sunlight or to smoky atmospheres may cause yellowing, so that the colour match with the natural skin should be reassessed from time to time. Similarly, the tissues adjacent to the prosthesis must be examined regularly, because they often have reduced sensation and may become affected by the prosthesis without the patient noticing. Despite these problems, psychologically these prostheses are enormously beneficial for the patient. Their lives are often dramatically transformed by having them fitted.

1.2.8 Breast Implants

Prosthetic breasts are mainly used to increase size, mainly for cosmetic reasons.[80] A significant number, however, are implanted for reconstruction following removal of breast tissue for health-related reasons, typically

Table 1.6 Types of breast implant.

Smooth gel-filled
Textured gel-filled
Polyurethane covered
Saline-filled

cancer. Breast implants come in a variety of designs, as listed in Table 1.6, but all involve a liquid inside an impervious sac. Of these, the smooth gel-filled implant is the most widely used.

The gel employed has typically been silicone fluid, but concerns have been expressed about leakage and for some years the United States FDA withheld their approval for these materials.[81] That situation has now changed, and these devices are approved once again and so available to patients.[82] Saline-filled implants have similar problems of leakage, even if there are no obvious defects in the outer sac. However, saline does not cause any adverse reaction in the surrounding tissue, so small amounts of such leakage can be accepted.[83] On the other hand, extensive leakage causes the implant to deflate, and then it must be replaced.

There are a number of complications that can arise with breast implants. The main one is the formation of fibrous capsule around the implant. In certain cases, this may become calcified, which needs further surgical intervention or removal of the implant.[84] The fibrous capsule may contract, resulting in disfigurement, implant migration and/or gross leakage.[85] This sort of contraction is much more likely with silicone-filled implants than with saline-filled ones, because of leakage of the silicone fluid in the former case.[86] Lastly, the presence of the fibrous capsule makes detection of breast cancer difficult,[85] and although there is no long-term indication of implants increasing the incidence of breast cancer, women with implants who develop breast cancer generally have more advanced disease than those without implants.

1.2.9 Ear Ossicles

The ear consists of three sections: the outer, the middle and the inner ear.[87] Sound is detected as the result of small waves of pressure in the air entering the outer ear and causing slight movements of the tympanic membrane (see Figure 1.6). These movements are transmitted along the ossicular chain, which comprises three tiny, lightly anchored bones, called the malleus, the incus and the stapes, respectively. Following transmission, the movement arrives at the oval window, a membrane that separates the middle ear from the inner ear, and here the movement becomes converted into electrical signals in the auditory nerve. These pass to the brain, where they are registered as sound.

Certain diseases may cause loss or damage to the ear ossicles and one solution is to employ biomaterials as ossicular prostheses. Implants have also been used to replace the bony auditory canal wall, which may have to be removed in radical mastoid surgery, although these have not been used as widely as artificial ossicles.

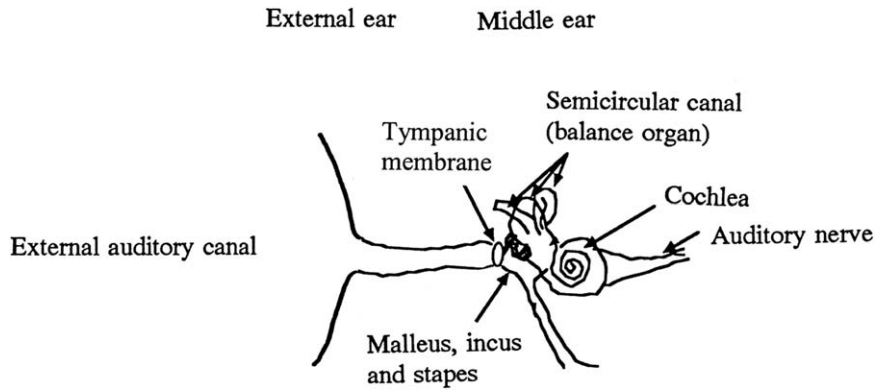

Figure 1.6 Structure of the ear.

Good results in terms of restoration of hearing can be achieved with synthetic materials, especially over the shorter term. Longer-term success is less easy, because implanted ossicles may suffer from infection, displacement and extrusion. A variety of materials have been used, including hydroxyapatite[88] and hydroxyapatite-filled polyethylene.[89] Ideally, biomaterials used in this application have mechanical properties that closely mimic those of natural bone, which is helpful because it reduces problems of displacement and extrusion. However, despite this, hydroxyapatite has not proved to be particularly successful, as it has extrusion rates of up to 15%.[90] More recently, titanium has been used to fabricate ear ossicles.[91] As it has proved in other applications, the titanium alloy is biocompatible when used for this purpose. Extrusion rates are low and although the metal is denser than natural bone, which results in the artificial ear ossicles being heavier than natural ones, clinical outcomes have been good.[91]

1.3 Conclusions

This chapter has described some of the most common surgical uses of artificial materials. The field is strongly interdisciplinary, and the chemical aspects of these materials are rarely considered. However, many of the problems in the field are predominantly chemical. These may arise from the composition of the material, from its degradation behaviour or from surface chemical effects. Success with implantable materials therefore needs an understanding of the appropriate chemistry. In the chapters that follow, both the chemistry of the interaction of materials with the body and of their composition and fabrication are described.

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