Chapter 15
Ophthalmic Biomaterials

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15.1 Introduction

Ophthalmology is a branch of medicine that has seen many technological advances in recent years. Lasers are used for imaging and treating many eye conditions, and their capabilities are further enhanced by computers and culminate in the integration of devices with neuronal elements to produce "artificial vision." In virtually all endeavors to develop therapies involving eye surgery, biomaterials play a central part [6, 15] (Fig. 15.1). Contact lenses are worn on the corneal surface to improve visual acuity in place of spectacles. Corneal implants, or keratoprostheses, have been designed to replace diseased or damaged cornea that have become opaque. Intraocular lenses are implanted following cataract surgery to replace the opaque crystalline lens. Viscoelastic substances have revolutionized cataract surgery enabling the first truly "keyhole" operations. Glaucoma filtration devices are used to produce a channel for the outflow of aqueous to prevent the increase in intraocular pressure. Tamponade agents are used to replace the vitreous and treat retinal detachments. Retinal implants are designed to transmit electrical signals to the brain via the retina and the optic nerve.

Biomaterials are exploited for their various physical properties to achieve the goals of surgery. The purpose of this chapter is not so much to enumerate the materials used, but to illustrate how treatment possibilities are being realized through an understanding of biological requirements and how these can be met by the appropriate choice of biomaterial. There are a number of essential requirements that need to be addressed by ophthalmic biomaterials which include the ability to deliver oxygen

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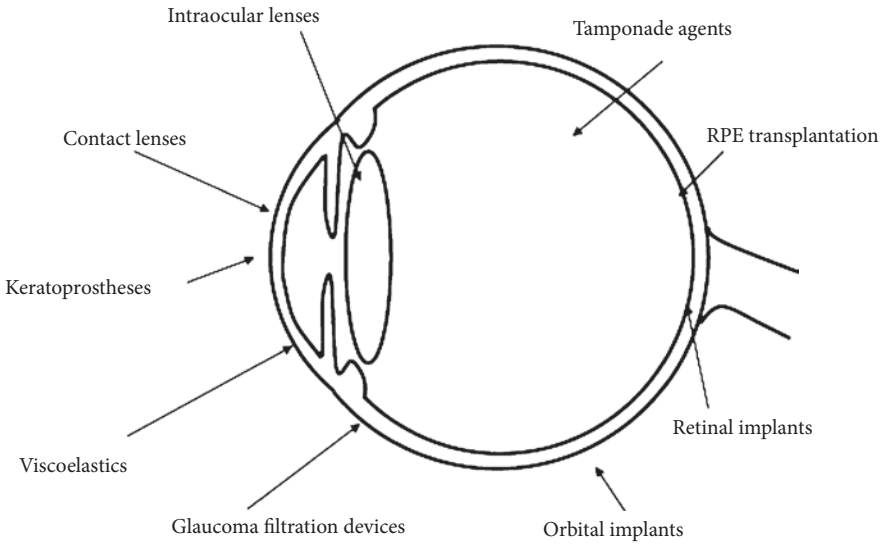

Fig. 15.1 The application of biomaterials in ophthalmology

to the tissues, modification of refraction, protection of tissues during surgery, integration with the tissue, modulation of wound healing, and tamponading of retinal breaks. This chapter will address each of these in turn and will discuss the disease processes, the requirements, and the biomaterials solutions under each category.

15.2 Oxygen Delivery

A fundamental property of all viable biological tissue is respiration. The delivery of oxygen throughout the body is usually via perfusion with blood vessels. There are however a few notable exceptions where tissues do not have a direct blood supply in terms of arteries, veins, or capillaries; these include the cornea in the eye and the cartilage in joints. Both tissues are bathed in fluids, and the oxygen dissolved in the fluids is capable of meeting the metabolic demands of the tissues. In the case of the cornea, it is bathed on the internal aspect by aqueous humor and on the external surface by the tear film.

The aqueous humor is produced by ciliary processes inside the eye. These are highly vascularized finger-like processes, and the aqueous is formed by a combined process of active transport and diffusion. There are constituents in the aqueous with much higher concentration than in blood; this includes substances like vitamin C and glutathione. Other dissolved substances such as oxygen and glucose simply go down the diffusion gradient to supply the cornea.

The cornea is lined on the inner aspect with a single layer of cells called endothelium. The substance of the cornea is called the stroma and is made up of extracellular material and collagen fibers. The collagen fibers are arranged in lamellae or

layers with precise spatial separation, the dimension of which is related to the wavelength of the visible spectrum of light. The endothelium keeps the cornea relatively dehydrated by an active transport mechanism. If for any reason the endothelium fails, the cornea will become edematous and lose its transparency. The external surface of the cornea is covered by a layer of epithelium. The cornea is also bathed with a film of tears. The tear film presents a smooth refractive surface for light to enter into the eye, and it transmits dissolved oxygen effectively to the corneal epithelium and stroma.

Covering the cornea by contact lenses potentially deprive the cornea of access to the oxygen supply dissolved in the tear film. The biomaterials used to make contact lenses deliver oxygen in different ways.

The number of people wearing contact lenses throughout the world is enormous, and the materials used in their manufacture have evolved since the 1930s. There are a number of important properties required of a material to be suitable for use as a contact lens. These include stability, being non-irritant, robustness for handling, wettability to maintain tear film, resistance to spoilation by components of the tear film, and most importantly oxygen permeability. Here we will consider particularly the way in which they influence oxygen delivery to the cornea.

The first readily available contact lenses were made of polymethylmethacrylate (PMMA) [2]. This had some very successful properties in terms of ease of manufacture to high tolerance, robustness for handling, and stability. Its intermediate wettability allowed sufficient tear film coverage, but its major drawback was the very poor oxygen permeability. This significantly restricted access of oxygen to the cornea. The route to overcome this problem was to make these PMMA lenses small so that they moved over the cornea during blinking thus allowing the tears to bathe the cornea. The problem with oxygen permeability led to the development of rigid gas-permeable lenses.

Rigid gas-permeable lenses are made by incorporating siloxane-based materials with the methacrylates, for example, methacryloxy-propyltris (trimethyl siloxy silane) (TRIS) [21]. These materials had significantly higher oxygen permeability, but the presence of the siloxane groups also increased their hydrophobicity, thus reducing the tear film interaction and increasing the spoilation of the lenses. It is generally found that hard lenses and the original PMMA ones are less comfortable for the wearer and take longer for the eye to become accustomed to them.

Soft contact lenses are significantly more comfortable for the wearer. There were originally two types of soft lenses, hydrogel and polydimethylsiloxane. The first hydrogel lenses were developed from polyhydroxyethylmethacrylate (pHEMA) with a water content varying around 38–80% [21]. This provided excellent wettability and thereby increased the comfort factor. Although the oxygen permeability of these lenses was significantly better than PMMA, it was afforded simply by the bulk water content and therefore increases in the oxygen permeability required higher water content and thinner lenses resulting in lenses that were more fragile and difficult to handle. Since the maximum oxygen permeability was limited by the water content of the gels, it was determined that these lenses were not suitable for extended wear use because the health of the cornea could not be guaranteed. Most hydrogel lenses available now are copolymers of pHEMA with, for example, methacrylic

acid (MAA), methylmethacrylate (MMA), or *N*-vinylpyrrolidone (NVP), and by adjusting the copolymer ratio, it is possible to optimize the lens properties in terms of the water content, durability, and strength. Many of these lenses are now marketed as disposable lenses and will be worn once and then thrown away.

Polydimethyl siloxane lenses have excellent oxygen permeability due to the bulky nature of the siloxane group and the high mobility of the polymer chains. They also have very good mechanical properties for ease of handling. Unfortunately the pendant methyl groups cause this material to be hydrophobic causing significant disruption of the tear film and also have a high susceptibility to lipid attachment and adhesion to the cornea. Attempts to increase the hydrophilicity of these lenses have been achieved by coating then with hydrogels or by gas plasma treatments.

Further developments in these devices then moved to exploring ways to incorporate components of both the hydrogels and the siloxane materials in an attempt to provide a material with both high oxygen permeability and high wettability. The development of silicone containing hydrogels has several difficulties including how to overcome the incompatibility for the hydrophobic and hydrophilic components during manufacture, which can lead to phase separation and consequent opacity. The key to achieving this has required the development of polymerization routes that allow the mixing of the hydrophobic and hydrophilic monomers. In contrast to the hydrogel lenses, which rely on the water content to increase oxygen permeability, these lenses rely on the silicone component, and increases in the hydrogel component will decrease the oxygen permeability. Unfortunately these copolymers form with the silicone component at the surface; thus they are hydrophobic and therefore suffer from the same problems as the pure silicone lenses. To overcome this, the surfaces can be modified to increase their hydrophilicity.

15.3 Refraction

The main conditions that we shall consider are myopia (short-sightedness), hypermetropia (long-sightedness), astigmatism, and aphakia (without a lens). These are generally referred to as refractive errors. It means that the optics of the eye cannot focus a clear image onto the retina. To understand why, it is necessary to know how light is refracted by the various structures of the eye.

The main refractive power of the eye is provided by the cornea and to a lesser extent by the crystalline lens inside the eye. The cornea has an external surface covered by a tear film. Light rays travel from air (usually) and are refracted by curvature of the tear film overlying the cornea and enter into the eye. Once inside, the light rays are marshalled by the pupil, which varies in size allowing different amount of light through to the crystalline lens. The substance of the cornea and the aqueous has a refractive index of about 1.3, whereas the crystalline lens has greater refractive index of 1.4. The lens presents a front curved surface such that the light rays entering the lens will be further refracted. The lens has an even more steeply curved back surface. As the light rays exit the lens and enter the vitreous humor, there is a change

in refractive index from 1.4 back to 1.3. The light rays are further refracted and travel through the vitreous cavity until they reach the retina. In a person with no refractive errors, the light rays will be refracted and be brought to focus on the retina, thus creating a clear image. When the optics of the eye fails to do this, refractive errors are said to occur.

The commonest refractive error is myopia. Myopia is often due to increased axial length; the eye is larger and the optics of the eye focuses the image of a distant object in front of the retina. By bringing the distant object nearer, the image can then be focused onto the retina. This is why myopia is also commonly called near or short-sightedness. The "opposite" situation is when the axial length of the eye is too short, such that a distant object is brought to focus "behind" the retina. This is referred to as hypermetropia. Most young patients are capable of increasing the refractive power of the eye by "accommodation." By exercising the ciliary muscles, the lens changes its shape and becomes more rounded, thus presenting a more curved surface to refract the light rays. Accommodation in the hypermetropic patient might bring a distant object into focus. There is however a limit to this accommodation, and it is therefore more difficult to focus an image the nearer it is to the hypermetropic eye. That is why hypermetropia is also called long-sightedness, as it is easier for these patients to focus distant objects than those closer to the eye.

So far we have alluded to refractive errors caused by the eye having axial lengths that are too long or too short. Refractive errors can also be caused by the cornea being either too curved or too flat. The cornea presents an air/tear film interface and is therefore responsible for most of the refractive power of the eye. If the corneal surface is not perfectly rounded but is elliptical instead, then the refractive power in one axis may be greater than another. This creates what is called astigmatism. A point source of light in the distance cannot be brought into a single point focus inside the eye. A small amount of astigmatism is present in almost every person.

Another common cause of refractive error is due to cataract extraction. Cataract is the cloudiness of the crystalline lens of the eye. When a cataract is removed, the eye is no longer capable of focusing an image; replacement of the refractive power is required. This is achieved usually by placing an artificial intraocular lens in the eye. The normal crystalline lens is capable of changing focus as we alluded to previously. As yet, there is no intraocular lens that is capable of producing a significant amount of focusing.

In the case of refractive error, the requirement is simple. The aim is to focus the image on the retina. This is usually straightforward when both eyes have the same refractive error. There are some instances when the two eyes have significantly different refractive error. For example, a patient can be myopic in both eyes, but only one eye develops a cataract. When the cataract is removed, one has an opportunity by using an intraocular lens to correct not just for the aphakia but also the myopia. If that is done, the un-operated eye will remain shortsighted, but the operated eye is in focus. This situation is called anisometropia, where the two eyes have significantly different refraction. The result of anisometropia is that the image size of an object cast on the retina can be significantly different between the two eyes. This difference in image size is referred to as aniseikonia. It has been estimated that the

brain can cope with up to 30% difference in the image sizes but beyond this a patient might experience confusion and double vision. So the requirements are not only to provide refractive power to correct for errors but also to balance the two eyes.

Hard contact lenses rest on a film of tears. The main refractive surface then becomes the front surface of the contact lens rather than the tear film overlying the cornea; however, the tear film between contact lens and the cornea is also a refractive tool. Its front surface conforms to the back surface of the hard contact lens; its back surface conforms to the front surface of the cornea. The tear film has a refractive index close to that of the cornea. It therefore effectively neutralizes the refractive power of the front surface of the cornea. The front surface of the tear film is of course perfectly rounded as it conforms perfectly to the back of the hard contact lens. Therefore, the tear film acts as an astigmatic lens, overcoming the imperfection of the curvature of the cornea, converting an elliptical surface to a perfectly rounded surface. Hard contact lenses, in particular rigid gas-permeable, for example, silicone/acrylates and fluorosilicone/acrylates [3], are therefore useful for correcting astigmatism and can achieve this correction to limited extent. Soft contact lenses are more flexible and conform to the shape of the cornea. There is less of a tear film between the soft contact lens and the cornea. It is therefore not generally suitable for patients with astigmatism caused by elliptical curvature of the cornea.

15.4 Tissue Protection

Modern cataract surgery is often described as small incision microsurgery. Indeed, the cataract operation is one of the first keyhole type surgeries. The cataract has the shape and size of a "Smartie," being about 10 mm in diameter and 6 mm in thickness. In a young person the lens is semi-solid and capable of altering its shape largely as a result of the elasticity of the lens capsule. When the lens turns cataractous in old age, it becomes very hard. Removing a lens in a child can be achieved by aspiration as the lens material is soft, and this can be done via a small incision. After the age of 40, most lenses are too hard to be removed simply by aspiration. With the advent of phacoemulsification, small incision surgery was made possible. A special probe can be inserted into the eye via a small incision. This probe has a needle, which vibrates at ultrasound frequency providing the energy necessary to break down and liquefy the hard nucleus of a cataractous lens. The needle has an outer sleeve that provides an infusion and cools the needle and prevents the ultrasound energy from burning the surrounding tissue. Modern cataract surgery is therefore an elegant operation and is highly effective. The small incision ensures rapid visual recovery and minimizes the distortion of the cornea that can produce undesirable astigmatism.

The use of ultrasound and the delivery of high energy into the anterior chamber are not without hazards. As described earlier, the cornea is made up of collagen fibers arranged in layers. The transparency of the cornea is thought to be critically dependent on the spacing of the layers of collagen, and when the cornea is water-

logged, it loses its transparency. The endothelium on the inner surface of the cornea plays a vital role in the active transport of water from the cornea. In adult life, the endothelial cells do not divide nor replenish themselves. With surgical trauma, such as bending and distorting the cornea, endothelial cells are lost and a major concern is that the use of phacoemulsification can significantly increase endothelial cell loss. If the cell count falls below a critical level, the endothelium can no longer maintain the clarity of the cornea.

Viscoelastics are used routinely in all cataract surgery. When injected into the anterior chamber, they coat the endothelium and absorb some of the ultrasound energy from the phacoemulsification probe. Furthermore, the viscoelastics are used to fill the anterior chamber to increase its depth such that instruments can be introduced without directly touching or damaging the endothelium. It is also injected between tissues as a spacer and provides a gentle way of separating them or holding structure back. The viscoelastics tend to stay together as a single bulk so any bleeding will not enter the substance of the viscoelastics; thus they help to maintain clarity, and when the anterior chamber is filled, it will not be obscured or stained by bleeding.

Viscoelastics are long chain polymers. Energy is dissipated through the relaxation processes in the long chain molecules of the viscoelastic substance; thus they are capable of damping vibrations. Viscoelastics have several other important properties. They are described as cohesive, dispersive, and viscous. Cohesive viscoelastic substances tend to have high molecular weights and high surface tension; they tend to stay together as a single bulk, but they tend not to coat the tissue. Dispersive viscoelastic substances tend to have lower molecular weights and lower surface tension; they adhere to structures and they spread and coat tissues. In general, more viscous substances tend to flow less well. Once injected into the anterior chamber, they can be relied on to keep it inflated long enough to carry out some surgical maneuvers, even though the pressure in the eye tends to push the viscoelastics out. Combinations of viscoelastic substances with different properties are sometimes used. The so-called "soft-shell" technique uses first a viscoelastic with good dispersive properties to coat, adhere, and protect the endothelium, and then, second, a viscoelastic with high viscosity and cohesive property is injected to keep the anterior chamber filled and inflated in order to carry out the phacoemulsification. Materials currently used in these products include hydroxypropylmethylcellulose, hyaluronic acid, chondroitin sulfate, polyacrylamide, collagen, and various mixtures of these materials in an attempt to optimize the dispersive and cohesive properties [1, 16].

15.5 Tissue Integration

The integration of biomaterials with the tissue is an essential element of the treatment for a number of eye conditions. To give some examples in this section, we will deal with keratoprostheses for a temporary or permanent artificial corneal trans-

plant, coral, or hydroxyapatite orbital implants following removal of the eyeball and a "chip camera" as a retinal implant for artificial vision. It has to be pointed out that both keratoprosthesis and retinal implants are some way from being successful in the sense that neither are readily available as a viable treatment as yet.

15.5.1 Artificial Cornea Transplants

The cornea can turn opaque and cause blindness commonly from infection, trauma, and some genetic eye condition. In the Western world, herpes simplex infection is common. Bacterial infections can lead to ulceration, and the subsequent healing gives rise to cloudiness and loss of vision. Xerophthalmia is a major cause of blindness in Africa and Latin America. It is associated with vitamin A deficiency and general malnutrition. Infection and trauma leads to scarring of the cornea as part of the healing process. Scarring of the cornea give rises to loss of transparency and to the development of new vessels. Corneas that are severely damaged can be treated with corneal transplant (penetrating keratoplasty). Transplant of any human tissues are associated with rejection as the body becomes sensitized and mounts an immune reaction against the transplanted tissue. Rejection of the cornea is particularly a problem with eyes that have developed new blood vessels. Transplant requires donors, and there has always been a shortage of donor material especially in third world countries. The sheer number of patients involved with corneal scarring diseases is such that it has long been imperative to find an artificial cornea graft or keratoprosthesis rather than to rely on donation from deceased donors.

The keratoprosthesis needs to be watertight since any leaks will give rise to portals for infection. By definition this requires the artificial cornea to integrate with the surrounding eye tissue, which are often abnormal and damaged by infection or trauma. For example, the eye often has abnormal lids that do not close properly, and the conjunctiva may be dry and contracted. The keratoprosthesis will have to be transparent to allow light to enter the eye for sight. If the eye is severely damaged, it may also not have a crystalline lens so in these situations the keratoprosthesis will need to have refractive power to substitute for the lack of a lens in the eye. Furthermore, ideally the outer surface should support a functional corneal epithelium. The response of corneal endothelial cells to the inner surface of the keratoprosthesis also needs to be controlled.

Early designs consisted of PMMA cylinders to act as the optically clear window and various mechanical means of anchoring this to the surrounding tissues, for example, the Dohlman "collar-button" keratoprosthesis. Clinical results from these devices are limited mainly due to lack of integration of the surrounding tissue with the device. Attempts to improve this were made by incorporating the PMMA optic in autologous tissue such as tooth as in the Strampelli osteo-odonto-keratoprosthesis [10].

The next generation of keratoprosthesis involved a move towards more flexible materials that would improve the mechanical integrity of the tissue/implant inter-

face. Initially these included various porous polymer skirts still attached to a rigid PMMA optic, but more recently the advantages of flexible materials for the optics have also been realized, for example, silicones and polyurethanes. The properties of the porous skirts require sufficient mechanical strength to withstand intraocular pressure and suturing to the surrounding tissue, and they should encourage keratocyte ingrowth, collagen deposition, and stabilization. Initially these were constructed from PTFE or carbon fiber-reinforced PTFE (Proplast), which were successful in terms of tissue ingrowth and suture placement. However, their attachment to a rigid PMMA optic was a recurring problem. Thus there was a focus of the research towards a one-piece, flexible design allowing tissue ingrowth directly into the device to produce a stable interface. Preliminary studies investigated the use of a device with a porous PTFE skirt, which was chemically bound to a transparent polyurethane elastomer optic with some success. Other combinations explored included silicone elastomer optics with carbon-fiber haptics and polypropylene/polybutylene skirts with PVA copolymer hydrogel central optics [5].

Major studies have evaluated the possible use of pHEMA in this application, in which the properties of the pHEMA can be controlled by the water content and they can be manufactured such that they consist of an outer poly HEMA sponge skirt which is fully integrated with a transparent optic [4].

In some situations, re-epithelialization of the keratoprosthesis surface is impractical owing to the underlying disease situation. If, however, appropriate ocular conditions apply, it would be a significant advantage if epithelialization of the surface could be achieved. The absence of this layer allows the entrance of bacteria and epithelial down-growth at the interface and inhibits spreading of the tear film. Current research to improve this process investigates the influence of surface properties and their modification on the epithelial cell adhesion and spreading [9].

15.5.2 Artificial Eye

The eye is sometimes removed as a whole because it contains a cancerous tumor or because of severe trauma. Severe injury can result in an eye that is not only blind but also painful. Healthy eyes have an intraocular pressure (IOP) as a result of the constant secretion of fluid (aqueous) by the ciliary processes within the eye. The fluid is drained away mainly via the anterior chamber angle; the drainage of the fluid against the resistance provided by the anterior chamber angle gives rise to the IOP. End-stage diseased eyes often have poor capacity to secrete fluid, and the eye as a result is soft and appears collapsed. Quite apart from any visible damage, the sunken eye socket will be unsightly.

There are three main requirements when an orbital implant is placed in the socket after an eyeball is removed. First, the implant must replace the lost volume. Second, the implant should be capable of some “eye” movements. Third, the implant should be integrated to be secure such that it would not extrude from the eye socket.

Replacement of the volume is important when an eye is removed. Otherwise the socket appears sunken and unsightly; the upper lid will have a deep groove and the face will look asymmetrical. The eyeball is normally about 5–6 mL in volume. An orbital implant is used to fill the majority of this volume, and a contact lens is used to cover this and improve the appearance.

The eyeball is attached by six "extra-ocular" muscles that move the eyeball as it looks in various directions. When the eye is removed surgically, the muscles are cut from the eye, and the optic nerve is then divided. The eyeball is replaced with an orbital implant, which is simply a spherical ball. This spherical ball is usually covered with donor sclera or with a polymer mesh. The muscles of the eyes are reconnected by sutures onto the surface of the covering so that when the other eye moves, the orbital implant also moves. When the patient wears a contact lens over the orbital implant, it gives the appearance that the two eyes are moving together. For small eye movements (looking say 30° in each direction), the "artificial eye" and the other eye usually move in a very realistic fashion, but the movement of the "artificial eye" is limited in extreme directions of gaze.

Although orbital implants are attached to the muscles and covered by subcutaneous tissue and conjunctiva, they have a tendency to extrude. Extrusion occurs when the tissue overlying the implant wear away or breakdown [17]. This can occur when there is infection or if the implant is too big (to get the maximum volume replacements, surgeons tend to use the largest possible implant). The rate of extrusion depends on surgical technique and there being sufficient tissue to cover the implant and close the wound without putting the tissues under undue pressure. The foreign body response to the implant plays a significant role in the extrusion process. In the past, all implants were made of PMMA, and the body tends to form a fibrous capsule and hold the implant in place. More recently, coralline hydroxyapatite (Fig. 15.2), alumina, and porous polyethylene have been used [19, 7]. Their porosity allows the ingrowth of blood vessels and scar tissues, thus improving the integration of the implant with the tissue. After integration has occurred, a hole is sometimes drilled into the implant, and a corresponding peg is made in the overlying contact lens. In this way, the orbital implant is directly connected to the contact lens, and the range of movement of the artificial eye is increased [18].

15.5.3 Retinal Implants

There are a number of degenerative retinal diseases that cause blindness. Some such as retinitis pigmentosa has a genetic underlying cause, and the photoreceptors and the underlying pigment epithelium are affected. In the last stages of the diseases, the blood vessels supplying the retina become thin, and the optic nerve appears atrophic. Despite these advanced degenerative changes, many of the retinal ganglion cells remain viable. The ganglion cells form the inner layer of the retina, and their axons normally carry signals to the brain via the optic nerve. In end-stage retinitis pigmentosa, the photoreceptors are atrophic and no longer react to light stimulation;

Fig. 15.2 Hydroxyapatite orbital implant

thus the eye is blind. With some of the ganglion cells remaining intact, it is possible to stimulate these cells directly electrically to produce the sensation of light. Access to the ganglion cells would be via the inner surface of the retina. This is known as the epiretinal approach. However, the normal retina is a network of cells that carries out signal processing locally before passing the information to the brain. This network is organized in such a way that it is particularly sensitive to the boundaries of light and dark and to the orientation and the movements of such boundaries. This local processing is designed to extract the most "important" information from images cast on the retina and to pass this information on to the brain via the optic nerve. If retinal implants [23] are used to stimulate the ganglion cells directly, this input is bypassing most of the cells within the retina thus removing this local image-processing step. Therefore this processing work has to be carried out externally by a computer. An alternative approach is to use subretinal implants. By placing the retinal implants under the retina, these devices make use of the network of cells to carry out the local processing of the image.

Retinal implants need to make good contact with the retina to facilitate electrical conduction. The implants need to be anchored in a stable fashion so that good electrical contact is maintained despite movement of the eyes and the head. The anchoring or attachment of the implant should not be simply mechanical, but ideally involve cellular integration, with neurons (glial cells) growing into the implant to ensure good conductivity. The implant should not ideally produce a local inflammatory and fibrous tissue response. If the glial tissues in contact with the implant are replaced by scar tissues (fibroblasts-like cells laying down collagen), then the conductivity would be reduced, and progressively larger currents would be necessary to stimulate the retina.

In the subretinal approach [20], an array of micro photodiodes is implanted under the retina sitting on the retinal pigment epithelium and assuming the role of the

photoreceptors. The micro photodiodes, therefore, process the incident light into electrical energy. The electrical energy is passed to the postsynaptic cells in the retina and thereby transferred to the optic nerve. The arrays of micro photodiodes are fabricated into discs in the order of 100 μm thick and 3 mm in diameter. These can be implanted subretinally either via the vitreous cavity or through the sclera. Prototype devices have been implanted in animals and have been well tolerated in terms of the tissue response to the materials although some degradation of the metal microelectrodes, usually manufactured from gold or silicon, has been reported. It has also been demonstrated that some improvement in visual perception is possible although it is not certain that this is a result of electrical stimulation of the retina by the device since the surgery itself could cause transient stimulation due to release of neurotrophic factors. Further it is debatable whether sufficient electrical energy is produced by the currently available micro photodiodes to stimulate the retinal neurons, and current research is developing secondary systems to amplify the response.

In the epiretinal approach, the implant (Fig. 15.3) is placed on the inner surface of the retina, and ganglion cells are directly stimulated. In this approach, therefore, the image has to be captured using a camera and processed to provide the properties of the image as a series of short current pulses. The camera is sometimes implanted in the lens capsule following lens extraction in a similar manner to cataract surgery. Intimate contact between the epiretinal implant and the ganglion cells is required for effective stimulation. It will be very important to maintain this during long-term implantation, and thus it will be necessary to limit tissue ingrowth between the implant and the retina as a result of the response to the materials and/or the stimulation.

Animal studies have shown that these devices are well tolerated and have been shown to cause local activation of the visual cortex, and preliminary clinical trials in blind patients have reported improved visual perception. Further technological advances in this area could lead to devices that could restore significant visual acuity to patients with degenerative diseases of the retina which are otherwise untreatable.

15.6 Modulation of Wound Healing

There are a number of instances where biomaterials are being used to modulate the wound healing response as part of a treatment process. This includes glaucoma filtration devices in which the control of fibrosis is used to allow fluid flow from the eye to control the IOP.

Glaucoma is a common ophthalmic disease, which results in the increase of IOP. This leads to damage to the optic nerve and significant loss of vision. Many glaucoma patients are successfully managed with a simple drug regime. For some patients, however, this does not control the IOP, and it is necessary to use a surgical procedure to release fluid from the back of the eye, bypassing the normal route for fluid flow from the back to the front of the eye. Trabeculectomy is the procedure of

Fig. 15.3 Uncapsulated version of an epiretinal retinal prosthesis with the microfabricated antenna coil for data and energy transfer and the electronic components of the transponder system (*top*) and the microelectrode array with its drivers (*bottom*). Polyimide is used as the basic material. (We acknowledge Professor Peter Walter and the EPI-RET III consortium for providing this figure)

choice but control of the fluid flow can be difficult and lead to hypotony of the eye. Implantation of glaucoma filtration devices is used to improve the control of the fluid flow.

Initially these devices were simple setons designed to maintain patency of the channel through the sclera/cornea into a subconjunctival bleb and involved materials such as silk, gold, platinum, and magnesium. These universally failed often due to a chronic inflammatory response leading to occlusion of the channel. Tube designs were developed using materials such as polyethylene, silicone, and

Fig. 15.4 Flexible plate Ahmed valve (kindly provided by Altomed Ltd, UK)

PMMA. The success of these tubes depended on the fibrosis formed in the subconjunctival space to control the hypotony [14].

In 1969 Molteno developed a tube and plate design, which forms the basis of the current devices in clinical use. The idea of this design was that the plate would control the fibrosis around the subconjunctival bleb to maintain the patency of the fluid flow out of the eye. Current devices (Fig. 15.4) are predominantly made from silicone, and various design modifications have been made to incorporate valves within them to control the outflow of fluid [12].

15.7 Interfacial Tension and Tamponade

Retinal detachment is an important cause of blindness in the Western world. It is the final common pathway for many disease processes including diabetic retinopathy and age-related macular degeneration. Retinal detachment is the separation of the neurosensory retina from the underlying pigment epithelium. The commonest reason for retinal detachment is that caused by a retinal break called rhegmatogenous retinal detachment.

The center of the eye is filled with a transparent jelly-like substance called the vitreous. The gel is made up of a network of long collagen fibers with glycoprotein such as hyaluronic acid bound to the collagen. The hyaluronic acid in turn binds to many molecules of water by non-covalent bonds leading to a gel which has 97% by weight of water giving the vitreous a jelly-like, semi-solid consistency. The vitreous moves as a single body when the eye moves, as it looks from one side to the other. The vitreous is normally attached loosely to the back of the lens and the whole surface of the retina and the optic nerve. With age and with certain conditions such as abnormally high degree of myopia, the vitreous gel loses its homogenous consis-

tency, and the collagen network collapses. The vitreous becomes detached from the optic nerve and the posterior retina while remaining attached to the retina and pars plana anteriorly. As a result, the vitreous no longer moves as a single body. With eye movement, the eye wall rotates, and the vitreous posteriorly lags behind creating what is referred to as dynamic traction. This vitreous traction is the cause of retina tears.

The collapse of the vitreous and its separation from the optic nerve and the surrounding retina are referred as Posterior Vitreous Detachment (PVD). The posterior chamber is now made up of the semi-solid vitreous gel immediately behind the lens and water-like fluid vitreous in front of the retina. Eye movements in addition to producing traction on the retina also create currents in the fluid vitreous. After a retinal break is formed, the fluid behind the vitreous is channeled through the retina break and causes the retina to be detached. The fluid vitreous underneath the retina is now referred to as subretinal fluid. The separation occurs at the level of the photoreceptors such that the neurosensory part of the retina (all the nerve cells) is lifted away from the underlying epithelial part of the retina (retinal pigment epithelium). Once detached, the photoreceptors become apoptotic within hours. For this reason, the treatment of retinal detachment is relatively urgent; otherwise there will be irreversible loss of vision. Thus a rhegmatogenous retinal detachment is caused by the combination of dynamic traction and currents in the fluid vitreous in the presence of a retinal break.

The treatment of retinal detachment aims at closure of the retinal breaks. The subretinal fluid can be drained away, but this may be unnecessary because once the retinal break is closed, the subretinal fluid will be carried away by active transport by the retinal pigment epithelial cells. Retinal breaks are closed in one of two ways: by external or internal tamponade. The word tamponade carries the meaning of "plugging." External tamponade refers to buckling of the sclera. In this process the full thickness of the eye wall, including the choroids and the retinal pigment epithelium, is "pushed in" to "plug" the retinal break. Scleral buckling is achieved by sutures and by the use of explants. The explants are made of either soft sponge-like silicone or more solid silastic material. Internal tamponade relies on the use of bubbles. The bubbles can be gas or liquid; they must be immiscible with water and form an interface with fluid vitreous. When injected into the vitreous cavity, they push against the retina "plugging" the opening thus preventing further liquid vitreous getting into the subretinal space.

The ability of a tamponade bubble to close retinal breaks depends crucially on the shape of the bubble. For example, if the bubble has a specific gravity close to that of the fluid vitreous, it will tend to remain spherical. This shape is not particularly useful because it makes only a small area of contact with the upper part of the retina. Thus positioning the bubble over the retinal tear requires the patient to position their head (and eye) in such a way in order to "float" the bubble against the correct part of the retina. Once the retinal break is closed, it needs to be "sealed" with retinopexy. Retinopexy is induced either by cryotherapy or laser photocoagulation. It causes controlled and localized tissue damage around the edge of the break.

The healing response causes an adhesion of the retina to its surrounding structure and thereby a watertight seal. This healing response takes 2 weeks or so to form.

The effectiveness is therefore dependent on the shape of the bubble. This in turn is dependent on the interfacial tension against water and on the specific gravity of the gas or liquid bubble. Of the two, specific gravity is much more important in determining the shape of the bubble. In the case of liquid tamponade agents, the viscosity becomes an important consideration. There are two groups of tamponade agents: the gases and silicone oils. They are all immiscible with water; the gases, however, are absorbable and will exit the eye. Silicone oils stay in the eye until they are removed usually 3–6 months after they have been injected although in some instances they are left in the eye permanently.

If an air bubble is used, the air will dissolve in the fluid vitreous and move down the concentration gradient into the bloodstream and be carried out of the eye. The bubble may not plug the retinal breaks long enough for the retinopexy to take effect, and the retina may become detached again. For this reason, gases such as sulfahexafluoride and perfluoropropane that are relative insoluble in water are used. This prolongs the retention of the bubble in the eye. Indeed, if a bubble of pure perfluoropropane is injected into the eye, dissolved nitrogen in the blood tends to move down the concentration gradient from the bloodstream into the bubble. The bubble will therefore expand in size until equilibrium is reached when the egression of dissolved gases is balanced against the entry of dissolved nitrogen from the eye. This expansion of the bubble can give rise to a dangerous rise in the pressure, so insoluble gases like perfluoropropane are normally diluted with air to a non-expansile concentration such that the bubble would be in equilibrium avoiding a possible rise in eye pressure.

All gaseous tamponades will eventually dissolve and come out of the eye. This usually takes a few days and at most a few weeks depending on the solubility and concentration of the gas used. For example, a bubble made up of 12% perfluoropropane and air can last up to 10 weeks inside the eye. The bubble will, however, get smaller and smaller such that it is not useful for supporting the upper part of the retina for much more than 3 weeks. Specifically, in cases of proliferative vitreoretinopathy (exaggerated healing response), scar tissues can pull on the retina to form new retinal breaks and give rise to recurrence of retinal detachment. In these instances, it is desirable to achieve a wide support of the retina for a prolonged period. For this a non-absorbable tamponade agent might be used which normally means silicone oils.

It is important to compare the behavior of the gases and silicone oil tamponades [22, 8]. Gas or gas air mixtures have high interfacial tension with water (e.g., 80 dynes/cm for air). They are expected to adopt a very rounded shape. But because the specific gravity is so low (approximately 0.001 g/mL), the buoyancy is very high. Instead of a spherical bubble, gas and air bubbles have the shape of spherical caps. Silicone oil has a relatively low interfacial tension (35 dynes/cm), but a specific gravity (0.97 g/mL) close to water (1 g/mL). Silicone bubbles are almost spherical. For any given volume of a bubble, the more spherical the bubble, the less area of the retina it is expected to tamponade (Fig. 15.5).

Both groups of tamponade agents have their advantages and their limitations. A bubble of gas with its spherical cap shape means that most of the volume of the tamponade is used to support the retina, but the bubble gets absorbed, and duration of tamponade is limited. A bubble of silicone does not get absorbed, and if the posterior segment of the eye is totally filled with silicone oil, then retinal breaks in all locations can be plugged. Randomized trials, however, failed to show silicone to be more effective than gas. One important reason for limitation of silicone oil is that it is not possible to totally fill the eye. Since the silicone oil bubble will maintain a spherical shape, any under fill will result in a significant area of the lower part of the retina, which is not tamponaded.

Silicone oil was first introduced as a possible tamponade agent in 1958 [6]. There have been several multi-center trials of silicone oil tamponades that have reported that retinal reattachment is achieved in the majority of eyes using vitrectomy and a

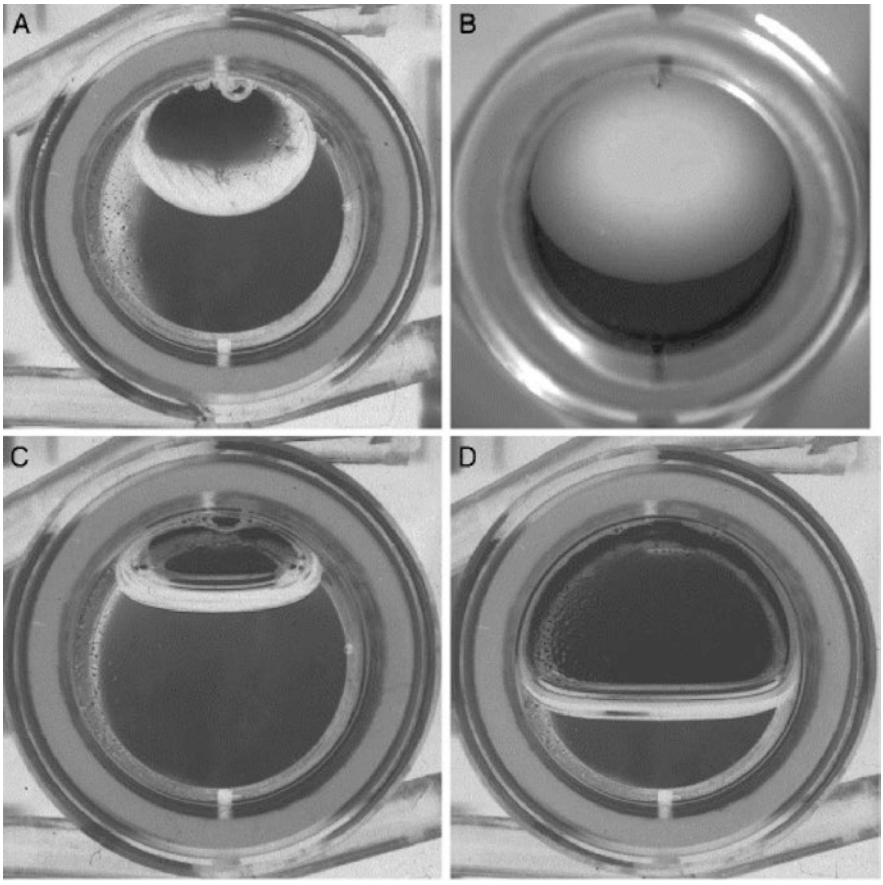

Fig. 15.5 Tamponade bubbles in a model eye chamber to illustrate the shape of the bubbler; (**a**) and (**b**) silicone oil bubbles, (**c**) and (**d**) air bubbles

silicone oil tamponade and that the visual outcome is acceptable. There are, however, also several case studies that demonstrate specific problems associated with the use of silicone oil. These include inflammatory responses, retinal toxicity, lack of tamponading, and emulsification.

For several years 1000cSt silicone oil was used clinically, and after varying periods of time, the oil was reported to emulsify in the eye. This caused three specific problems; first the emulsion could not tamponade the retina, second the emulsified droplets caused a clouding of the vision, and third the emulsified droplets could stimulate adverse biological responses including inflammatory reactions and blocking of the fluid outflow from the eye. To reduce the risk of emulsification, 5000cSt silicone oil is now advocated for clinical use. However, the high shear viscosity of this oil significantly increases the difficulty of injecting the tamponade agent into the eye and its removal after the retina has reattached.

To tamponade retinal breaks in the lower segment of the retina, it was necessary to find a tamponade agent that was heavier than water. Perfluorocarbon (PFC) with more than a five-carbon chain are liquids at room temperature. They are immiscible with water and having been originally investigated as blood substitutes have been shown to be non-toxic. PFCs are substances composed of a carbon backbone saturated with fluorine atoms. They are typically formed by fluorination of parent hydrocarbons. A range of PFCs is currently available for clinical ophthalmology applications

They are optically clear and their refractive index varies between 1.2 and 1.3. This property allows visualization of the retina through the PFC bubble. In practice it is desirable for an intraoperative tool to have a refractive index different to that of water (1.33), so that the interface between the agent and the infusion fluid can be seen during the vitreoretinal procedure. As a tamponade, it is desirable for the agent to have refractive index closer to water so that the eye would undergo minimal refractive change postoperatively. The specific gravity of PFCs is in the range 1.7–2 g/cm^3, and thus they are significantly higher than water. So they will sink below water, but also the buoyancy forces will be significantly higher; thus the bubbles will be flattened, increasing the contact between the retina and the tamponade agent. In addition, they are less hydrophobic than silicone oil and therefore will make more contact with the hydrophilic retina than silicone oils due to their interfacial energetics alone. However, their hydrophobic nature limits their passage through retinal breaks and increases the effectiveness of the PFC in providing intraocular tamponade to retinal breaks. PFCs have low viscosity (0.8–8.0 mPas), and although this property facilitates the injection and removal of the PFC through small-bore instruments during the surgery, it also increases their tendency to disperse into small bubbles.

Although PFCs have been shown to be non-toxic chemically, the retina under them have been reported to suffer irreversible damage. It is believed that the high difference in specific gravity of these material and water could cause this damage either because the pressure on the retina is too high or that they are too effective at excluding water from the retinal tissue. Recent studies would suggest that the latter is more likely to be the cause.

The lack of short-term toxicity makes them ideal intraoperative tools, for example, to unfold retina, the removal of subretinal fluid, and the flotation and removal of dislocated intraocular lens components. At the end of the procedure, they are removed and replaced with a tamponade agent that can remain in the eye for extended periods of time, for example, silicone oil.

More recently semifluorinated alkanes (SFA) have been developed as tamponade agents [13, 11]. They are transparent liquids that are immiscible with water. In terms of their interfacial energetics, they are amphiphilic in that they have both a hydrocarbon end that is hydrophobic and a fluorocarbon end that is less hydrophobic. Measured against water, their interfacial energetics is similar but slightly lower than that of PFCs. They have a lower specific gravity than the PFCs at between 1.2 and 1.7 g/cm^3, and thus, although they will sink below the remaining aqueous, the buoyancy forces will be less and therefore the bubbles will be more rounded than the same volume of PFC. These materials have low viscosities of around 2.5 mPas, making them easy to inject and remove through small-bore instruments but susceptible to emulsification.

The amphiphilic properties of the SFAs make them soluble in PFCs, hydrocarbons, and silicone oil. It has recently been considered that it would be possible to take advantage of this property and mix SFAs with other tamponade agents, for example, silicone oil, to attempt to make a tamponade agent that has the advantageous properties of each material and overcomes the disadvantages of each.

The complete solubility of SFA in silicone oil can be produced in the laboratory. By mixing these materials in different ratios, it is possible to produce fluids with different specific gravities. Several of these materials are available with a range of properties controlled by the ratio of the two components. These have the advantage of being heavier than water but with a lower buoyancy force in comparison with SFA or PFC alone. They also have a significantly increased viscosity in comparison with the pure SFA and PFCs making them potentially less susceptible to emulsification, while at the same time they are less viscous than pure silicone oil, thus making them easier to handle. Thus these mixtures have the potential to overcome two of the disadvantages of pure SFAs and silicone oil. That is they will gently tamponade the inferior retina owing to the fact that their specific gravity is only slightly higher than that of water, and they have a viscosity in a useful range. Unfortunately because of the chemical structure, the interfacial energetics of the mixtures mimic those of silicone oil, i.e., highly hydrophobic rather than the less hydrophobic SFA. The interfacial energetics cause the SFA/silicone oil mixture to behave in a similar manner to pure silicone oil, that is, they will make poor contact with the retina and they will not fit well into recesses formed by scleral explants. However it is expected that they will be as effective as silicone oil in the inferior section of the cavity, and a thin layer of aqueous around most of the bubble could be beneficial in terms of the health of the retina.

15.8 Concluding Remarks

Biomaterials have made huge contributions to advances in ophthalmology with viscoelastics, intraocular lens, and contact lenses being notable examples. There are areas where progress has led to recent developments, for example, the introduction of heavy liquids and heavy silicone oils for the treatment of retinal detachments. There are, however, many difficulties to overcome before artificial vision can be achieved through the use of retinal implants. These challenges can only be met by the combined effort of clinicians, biologists, computer scientists, and bioengineers. Undoubtedly, further understanding of the role that biomaterials have in these devices will lead to success in the future.

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