Intraocular Drug Delivery Systems:

New Treatments for Eye Disease

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Matthew Avery

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Who needs to see anyhow?

The eye is fundamentally one of the most important organs during life. Because of aging, diseases and other factors which can adversely affect vision, the ability to maintain the health of the eye becomes all important. A leading cause of blindness is the inability in the treatment of eye diseases to introduce drugs or therapeutic agents into the eye.[1] Oral ingestion of a drug, or injection of a drug at a site other then the eye, does not provide effective levels of the drug specifically to the eye. On the other hand, when a drug is injected into the eye, it quickly washes out from within the eye into the general circulation. From the therapeutic standpoint, this may be as difficult as giving no drug at all. Because of this inherent difficulty of delivering drugs into the eye, successful medical treatment of ocular diseases is inadequate.

The need for a solution is even more pressing in that the cause of a number of ocular diseases have now been identified and many are treatable if a proper mode of therapeutic drug delivery is available. It is therefore of great interest to develop modes of treatment which overcome the limitations of present modes of therapy.

The eye at a glance.

Before discussing methods of treating ocular disease, the basic anatomy of the eye must be understood. The most important parts of the eye are the cornea, iris, pupil, lens, retina and sclera. All these parts can be seen on the diagram of the eye at the end of this paper. The cornea is the most anterior, transparent tissue of the eye, and provides two-thirds of the focusing power for the eye. The iris is circular, colored portion of the eye, which adjusts size to allow varying amounts of light into the eye. The pupil is then considered to be the hole in the center of the iris (though the pupil is really just the area in

the middle of the iris where there is no iris and is not really a separate part of the eye). Behind the iris, the pupil allow light to go through the iris and into the lens. The lens is transparent and curved on both sides and provides one-third of the refracting power of the eye. Light coming from the lens focuses on the retina, which is neural tissue lining the interior of the eye. Essentially transparent except for the blood vessels on its inner surface, the retina sends visual signals to the brain via the optic nerve. The sclera is the thick, white, outer coat of the eye that is attached to the ocular muscles which control the movement of the eye.[2]

What is an intraocular drug delivery system?

An intraocular drug deliver system (DDS) refers to a device that is surgically implanted into your eye and then ideally would constantly releases drugs for a set time. This includes both biodegradable and non-biodegradable devices, and the development of these devices will be discussed in the following sections of this paper. This device would be used to treat various eye diseases that are otherwise untreatable or difficult to treat with traditional therapies.

Traditional therapies include topical applications of drugs with eye drops. In general, this is very ineffective since the eye washes itself out quickly with tears, removing the drug from the eye. Additionally, topical applications of drugs to the eye are ineffective since diffusion of drugs through the cornea is difficult, making it almost impossible for a therapeutic amount of drugs to get into the eye and remain there for a significant amount of time.

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[1] Wong V. United States Patent, #5164188. 1992.
[2] Bradford CA. Basic ophthalmology. San Francisco: American Academy of Ophthalmology, 1999.

More effective traditional therapies of delivering drugs to the eye include intravenous (into the blood) and intravitreal (into the eye) injections. The main problem with both of these methods is that after a drug is injected, its concentration in the system decreases exponentially with time as the body consumes it. This means that to maintain clinically helpful concentration of a drug in your eye, frequent injections of the drug are required. Also for specific cases, both methods have other negative side effects. These are discussed below in a case study of the development of treatment of cytomegalovirus retinitis. Clinical treatment of the disease progressed from intravenous to intravitreal drug delivery, and finally to an intraocular drug deliver device.

How important is your sight?

Blindness, or fear of becoming blind, is a leading cause of suicide in people with AIDS.[3] This blindness is most frequently caused by cytomegalovirus (CMV) retinitis, which is a opportunistic ocular infection, that when left untreated, causes loss of vision and ultimately leads to blindness. Approximately 20% of patients with AIDS develop CMV retinitis at some time in their lives.[4] The increasing life expectancy of patients with AIDS, due to advances in treatment, means that blindness from CMV retinitis threatens to become even more common.

Treatment with sodium ganciclovir is effective in treatment of CMV retinitis, but requires frequent dosing. After the CMV retinitis is cured, lifetime maintenance on ganciclovir is required to prevent a relapse of the disease. When ganciclovir treatment is stopped, virtually all patients relapse within 3 to 4 weeks. Ganciclovir can be administered intravenously, but systemic ganciclovir cannot be taken concurrently with

[3] Culbertson WW. “Infections of the retina in AIDS patients,” *Int Ophtalmol Clin*. 1985;92:472-484.

zidovudine (better known as AZT), which is the leading treatment for patients with HIV.[5] Systemic ganciclovir has also been shown to cause neutropenia in approximately one third of patients.[6] Frequent intravenous injections can very inconvenient for the patient though. In addition to having to regularly see a doctor for the injections, the systemic application of ganciclovir requires large quantities of the drug to be used in order to get high enough concentrations of the drug in the eye.

To prevent the systemic side effects of intravenous ganciclovir, some doctors began treating CMV retinitis with intravitreal ganciclovir.[7] This has the advantage of allowing much smaller doses of ganciclovir to be used in treating the infection. Instead of having to use 0.7 g per intravenous injection, only 100 μg of ganciclovir needs to be used for an intravitreal injection.[8] Intravitreal ganciclovir also allows AZT to continue to be taken safely by the patient. This method of administering ganciclovir also reduces the number of visits to the doctor required. Intravenous ganciclovir needs to be administered two to three times a week, while intravitreal ganciclovir only needs to be received once a week. The problem with intravitreal treatment is that continuous injections into the eye eventually cause the eye to hemorrhage or lead to retinal detachment, where the retina become separated from the back of the eye. Both conditions can cause serious vision loss or blindness.

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[4] Jabs DA, Enger C, Bartlett JG. "Cytomegalovirus retinitis and acquired immunodeficiency syndrome," *Archives of Ophthalmology*. 1989;107:75-80.
[5] Freeman WR. "Intraocular antiviral therapy," *Archives of Ophthalmology*. 1989;107:1737-1739.
[6] Holland GN, et al. "Treatment of cytomegalovirus retinopathy with ganciclovir," *Ophthalmology*. 1987;94:432-434.
[7] Cochereau-Massin I, et al. "Efficacy and tolerance of intravitreal ganciclovir," *Ophthalmology*. 1991;98:1348-1355.
[8] Sanborn, GE, et al. "Sustained-release ganciclovir therapy for treatment of cytomegalovirus retinitis," *Archives of Ophthalmology*. 1992;110:188-194.

It is apparent that alternative system of administering ganciclovir is needed. Both intravenous and intravitreal delivery of the drug have serious side effects. As a solution, researchers developed an intraocular sustained-release device for delivering ganciclovir. The device consists of a small disk of ganciclovir, coated with ethylene vinyl acetate everywhere except on its top surface.[9] The top surface is covered with a permeable polymer layer which allows the ganciclovir to diffuse through it. A suturing strip of polyvinyl alcohol is also attached to the bottom surface of the device. This device is then surgically implanted into the vitreous cavity and sutured to the sclera with nylon thread. All these materials are non-biodegradable and biocompatible, meaning they will not dissolve and they will not be rejected by the body's immune system.

Once surgically implanted in a patient with CMV retinitis, this device functions by allowing ganciclovir to continuously diffuse into the interior of the eye. The device releases ganciclovir at a steady rate over approximately 12 months, and reaches effective therapeutic concentrations for treating CMV retinitis. The diffusion of the ganciclovir through the polymer membrane into the vitreous cavity happens at a constant rate, where the total amount of drug released follows first-order kinetics with respect to time. The first-order kinetics are followed until approximately 90% of the ganciclovir is consumed, at which point the concentration of ganciclovir in the eye drops off exponentially with time.[10] Once the device is implanted and drugs begin diffusing through the polymer membrane, the concentration of ganciclovir in the eye quickly reaches steady-state and the concentration of the drug remains nearly constant through the lifetime of the device.

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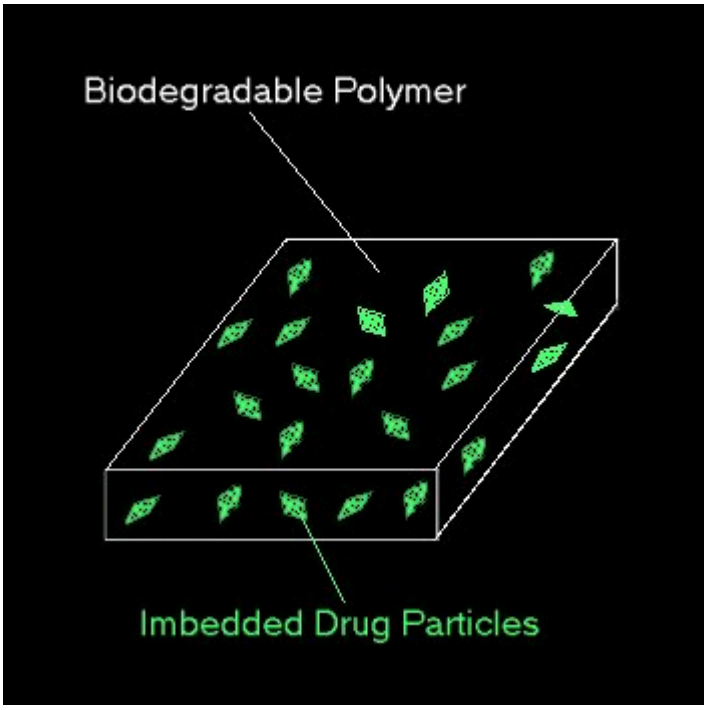
[9] Smith TJ, et al. "Intravitreal sustained-release ganciclovir," *Archives of Ophthalmology*. 1992,110:255-258.
[10] See [7] above.

After the ganciclovir is depleted, the device can be easily replaced with a short surgical procedure that has few apparent ill effects.

This intravitreal drug-release device was a significant development in ocular drug-delivery systems. It allows a local and continuous application of ganciclovir to the eye, which is superior to intravitreal and intravenous therapy. This device avoids the problems associated with systemic application of ganciclovir intravenously and the problems of neutropenia and retinal detachment caused by repeated intravitreal injections. This drug delivery system is currently used to treat CMV retinitis and research is being done to apply the technology to a variety of eye diseases.

Is there a better intraocular drug delivery system?

There is an obvious problem with the intraocular DDS described above though. When the drugs run out, you have to cut open the eye again to remove he device. An ingenuous solution to this problem has been developed. Oculex Pharmaceuticals, Inc. has developed a biodegradable ocular implant so that you don't have to worry about surgery to remove the drug delivery device; it just disintegrates away eventually.



The device can be as small as a grain of sand or as large as one-quarter the diameter of your eye, and is in the shape of a sheet or plaque. It is made from a homogenous mixture of both the drug and a biodegradable

polymer.[11] As the polymer dissolves, captured particles of the drug get exposed to the fluids of the eye and dissolve, releasing the drug into the eye. The polymer dissolves at a constant rate and therefore the drugs get administered to the eye at a constant rate. By altering the surface area of the plaque, you can control the rate at which the drug is released and by altering the thickness of the plaque, you can control the length of time you wish the drugs to be delivered. The device doesn't need to be surgically attached to the eye. It is designed so that all that needs to be done is to have the plaque placed against the interior of the eye, and it sticks and won't migrate around the interior of the eye.[12] The method by which the device attaches itself to the interior of the eye is proprietary knowledge of Oculex and is not included in this paper, though the fact that it is capable of doing this should be considered a remarkable property of the device. The known details of the device are discussed below.

This biodegradable ocular implant consists of a homogenous mixture of a therapeutic drug dispersed in a polymer matrix. Ideally, the therapeutic drug is fully immobilized in the biodegradable polymer so that diffusional release of the drug is minimal. It is also desirable to have the biodegradation process confined to the outer surface of the device.[13] Under these conditions, release of a therapeutic drug physically incorporated into the matrix is controlled solely by matrix erosion and because erosion occurs only in the surface layers, the kinetics of drug release are predictable and can be precisely controlled.[14]

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[11] Wong, V. United States Patent, #4997652. 1989.
[12] Gin, Jeremy. Interview with Oculex employee. 1999, April 27.
[13] Heller J. "Controlled drug release from poly(ortho esters)- a surface eroding polymer," *Journal of Controlled Release*. 1985;2:167-177.
[14] Heller J. "Controlled release of biologically active compounds from bioerodible polymers," *Biomaterials*. 1980;1:51-57.

A further consequence of surface erosion is that rate of drug release is directly proportional to the concentration of the drug in the matrix and to the total surface area of the device. Furthermore, because erosion of he device occurs by the uniform movement of an eroding front, the lifetime of the device is directly proportional to the thickness of the device. This is presuming that the total surface area of the device remains constant. In general, since the thickness of the device is much smaller then the other dimensions of the device, all erosion can be assumed to occur at only the two largest surface areas of the device (i.e. the front and back of the device). Since the surface area of the sides of the device are much smaller then the surface area of the front and back of the device, it can be approximated that the surface area of the device remains constant.[15] To ensure this, the area of erosion can be kept constant by coating the edges of the device with a biodegradable polymer with a much longer lifetime then the polymer in the matrix. The half-life of the coating on the edge should have at least twice the half-life of the matrix polymer, and preferably 4 to 6 times the half-life of the matrix polymer.[16]

Though the exact composition of the polymer matrix and the design of the device are proprietary information of Oculex, and therefore not publicly known, the basic principles of the device are known. The polymer, Supra, set forth by Heller[17] is suggested in the patents by Oculex as a possible matrix polymer, and the properties of this type of polymer will be examined below.[18]

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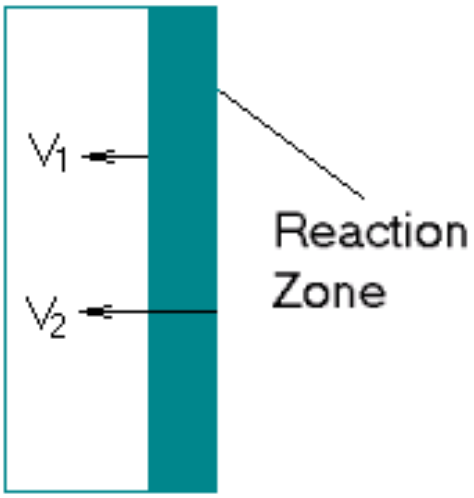
[15] See [12] above.
[16] See [11] above.
[17] Heller J. "Biodegradable polymers in controlled drug delivery," *CRC Critical Reviews in Therapeutic Drug Carrier Systems*. 1987;1:39-90.
[18] See [1] above.

The basic property of the device is that it only biodegrades at its surface layer. In general, this biodegradation would be caused by a hydrolysis reaction at the surface of the polymer that breaks the carbon backbone in the polymer chains. However the rate at which water intrudes into the polymer is an extremely important consideration, and the erosion process is defined in terms of the relative movement of two fronts: V_1, the rate of water intrusion, and V_2, the rate of polymer erosion. If $V_1>V_2$, the thickness of the reaction zone will gradually increase and eventually the matrix will become completely permeated by water, leading to an eventual bulk erosion process. If $V_2>V_1$, a surface erosion process will take place, but the rate of polymer erosion will be completely determined by the rate at which water intrudes into the polymer.[19] The diagram above illustrates this case.



Schematic representation of water intrusion and erosion for one side of a bioerodible device.

Therefore the design of this device must include a polymer with a degree of hydrophobicity, such that V_2 is somewhat larger then V_1, so that the rate of polymer erosion is limited by the rate of water intrusion. This allows devices to be created with long useful lifetimes and that are resistant to bulk erosion.

This biodegradable DDS created by Oculex is a revolutionary development in the treatment of ocular diseases. Previously, one of the greatest challenge that ophthalmologists have faced in treating ocular diseases is administering therapeutic drugs to the eye. With the development of this drug delivery system, ophthalmologists will now be able to effectively deliver drugs to the eye to successfully treat ocular conditions.

Obviously the biodegradable ocular drug deliver device is superior to the non-biodegradable ocular implant because surgery is not necessary to remove the device later, nor is it necessary to surgically suture the device to the interior of your eye. Additionally, this device is superior to intravenous and intravitreal therapies since it provide local, continuous application of the drug to the eye as opposed to systemic and/or fluctuating drug delivery.

So when do I get to stick one of these in my eye?

Currently the first product being developed by Oculex is in the final stages of phase III FDA human trial. Therefore the device should be available within the next couple years.[20] Their first product, called Surodex, is a device, as described above, that contains the generic anti-inflammatory drug, dexamethasone. It is being developed to be used to alleviate inflammation that occurs after cataract surgery.[21]

A cataract is any clouding or discoloration of the normally clear and transparent lens of the eye. Eyes with cataracts can be seen on Slides 1 and 2 on the next page. The normal lens continues to grow throughout life, and a cataract develops in almost all people as the eye ages. The lens consists of 35% protein by mass, and as the eye grows while you age, insoluble proteins tend to accumulate in the lens.[22] As the concentration of insoluble protein increases, the lens becomes more opaque and a cataract develops. Some degree of cataract formation is to be expected in all people over the age of 70. Age-related cataract occurs in about 50% of people between the ages of 65 and 74, and in about 70% of those over the age of 75. Cataract is the most common cause of decreased

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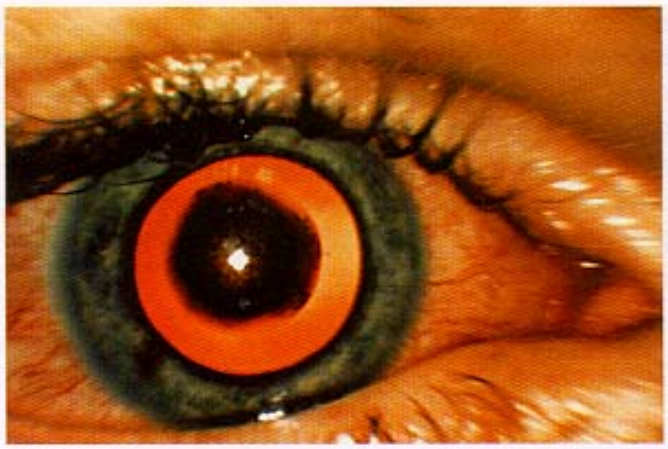
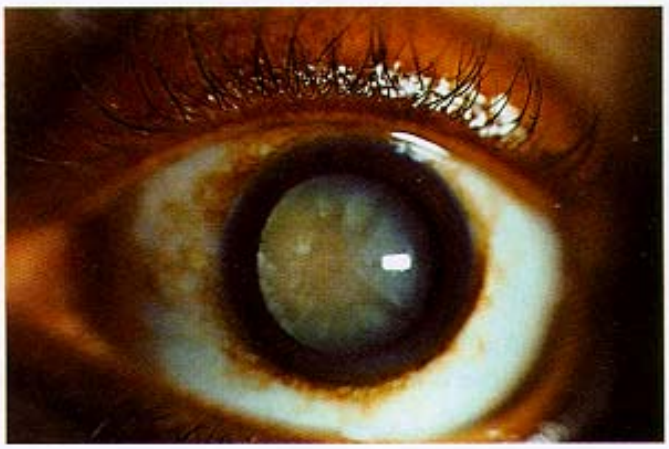
[19] See [13] above.
[20] Oculex Pharmaceuticals, Inc. http://www.oculex.com. 1999.
[21] See [20] above.
[22] See [2] above.

vision (not correctable with glasses) in the United States. However, it is one of the most successfully treated conditions in all of surgery, with approximately 1.4 million cataract extraction done each year in the United States.

After cataract surgery, all patients experience a painful inflammation of the eye for several months. The most common treatment of this inflammation is to use dexamethasone eye drops, which must be administered five times a day for a period of weeks or months. As discussed earlier, topical applications of drugs tends to be very ineffective. Surodex can instead be placed in the anterior chamber of the eye during cataract surgery, where it can provide controlled release of dexamethasone at therapeutic, non-fluctuating levels.[23] Phase II clinical trial have shown that a significant reduction of inflammation is achieved four days after surgery. By comparison, it took over four weeks for patients receiving dexamethasone eye drops to experience the same alleviation of



Slide 1 Immature cataract. The nucleus of this lens is opaque (nuclear cataract), while the cortical layers remain clear. The opacity appears as a dark shadow against the red reflex. This particular cataract, which is congenital, will obstruct vision more when the pupil is small than when it is dilated, as shown here.



Slide 2 Mature cataract. A cataract is called *mature* when the lens is totally opacified. A red reflex cannot be obtained; the pupil appears white. The radial spokes in this figure reflect variations in density of the radially arranged fibers in the cortical layers of the lens. Light still reaching the retina is totally diffused and will allow the perception of light but not form.

inflammation. These results show that using the biodegradable ocular implant is significantly more effective then administering drugs topically.

This application of this technology to treating other serious and potentially blinding ocular diseases is being researched. After Surodex is released, Oculex plans to establish alliances with pharmaceutical companies to develop devices to treat such diseases as age-related macular degeneration, diabetic retinopathy, and CMV retinitis. In addition to treating ocular diseases, this technology may have applications in treating conditions in a variety of places where it is difficult to directly administer drugs, such as the inner ear. In short, this technology has the capability to revolutionize the way drugs are delivered to the body.

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[23] See [20] above.

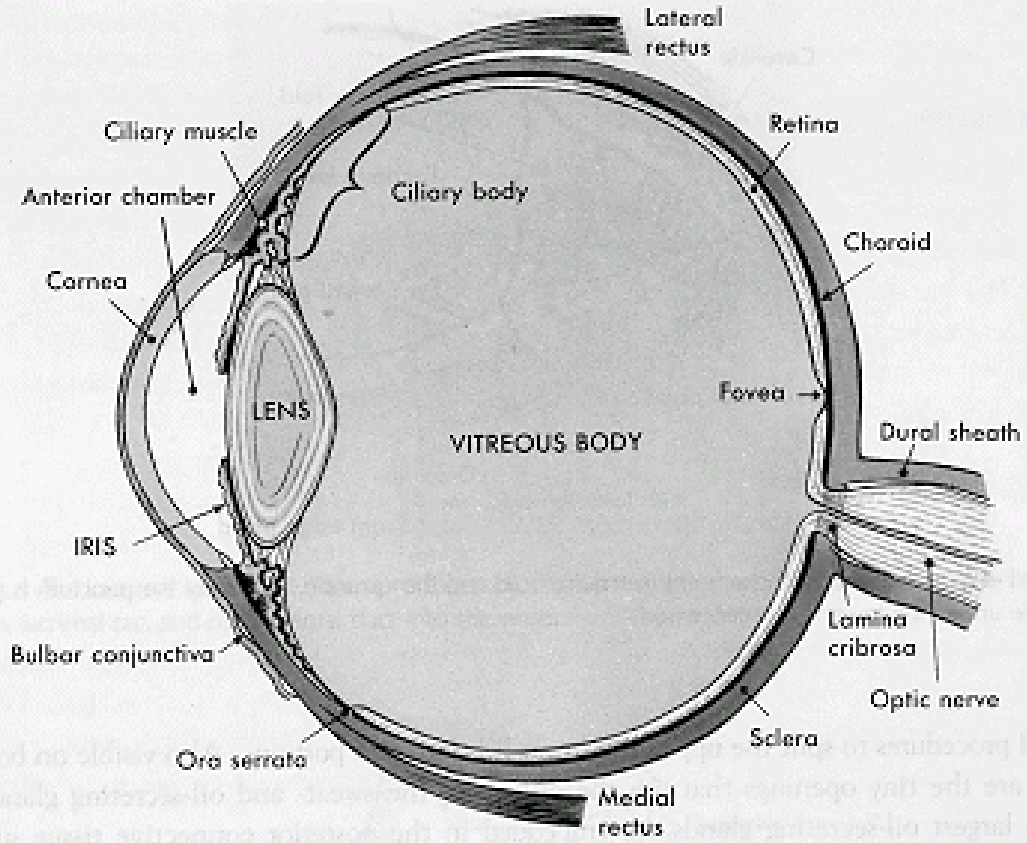

Fig. 1-2 The eye cut in horizontal section.

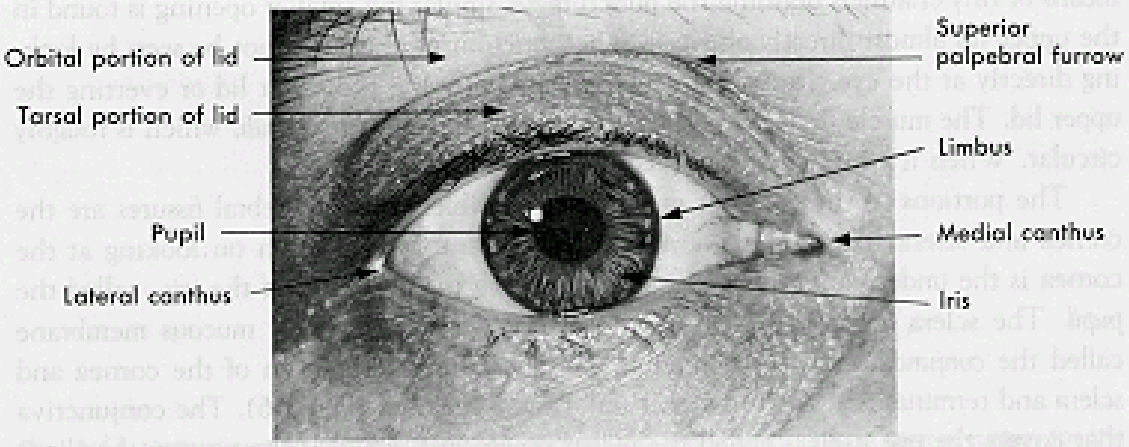

Fig. 1-3 Surface anatomy of the eye.

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Wong V. United States Patent, #4853224. 1987.

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