Haven't I seen this before?

In developed countries, cataracts are routinely replaced with intraocular lenses (IOLs). But developing an IOL that works for older, long-sighted patients is much more of a challenge. Kenn Hodd takes a look at the development of IOL materials and reports on lenses that could let a 60-year-old see like they could when they were 20.

By 2020 the global population of cataract-prone over 60s will number around one billion. By then cataract patients in the west could expect their eyesight to be equivalent to a 20-year-olds, after correction with an intraocular lens (IOL). It is also likely that the old joke 'my arms aren't long enough to read the paper' will be defunct, as the replacement lens will also be able to adjust its focal length, or accommodate for near as well as far vision in cataractous eyes – the holy grail in IOL research (see box below).

In just over five decades the implantation of an IOL has developed from being a difficult and hazardous surgical experiment, to the most common and highly-valued long-term medical implant. The potential market for implants is huge – WHO estimated that in 2000 more than 20 million people were blinded by cataracts, most of whom live in India, China and other less economically developed countries, figure 1. In developed nations the removal of a cataract and its replacement with an IOL is the norm, but in some countries a cataract may still be removed using the non-surgical technique of poking the lens with a stick! During the last decade major western lens manufacturers have been moving into the large markets of India and China, usually in collaboration with local manufacturers. Eye care is improving worldwide and the lens implant market is expected to be worth US$2.5 billion by 2005.

What is a cataract?

According to NHS Direct, 'a cataract is a clouding or whitening of the internal crystalline focusing lens of the eye. This lens is situated behind the coloured iris of the eye and light reaches it through the pupil. The cataract forms as a result of changes in the orderly arrangement of the transparent fibres from which the lens is made. Some degree of loss of lens clarity is present in almost everyone over the age of about 60'. Cataract surgery and related interventions have benefits that reach further than simply improving or restoring vision. Improved vision may delay the course of senile dimension in at-risk patients, and specially-designed phakic IOLs show promise in correcting myopia and hyperopia in younger patients.

How does an eye accommodate (focus)?

Accommodation is contraction of the ciliary muscle that relaxes the zonules suspending the eye's lens. This reduces the stress on the anterior capsular surface, which becomes more convex, increasing the lens power. Loss of the ability to accommodate occurs at about the age of 40 as with ageing the lens thickens and stiffens, to the point where the ciliary muscle's stress can no longer deflect the lens enough to accommodate.

From solid to folding IOLs

The concept of an artificial lens has been around for hundreds of years, but as with many products, it took developments in materials science to catch up before an impact was made.

A glass lens was tested in Germany in 1795 with disasterous results – the weight of the lens caused it to displace in the eye. There was a long lull in development until the production of a polymeric lens. UK ophthalmologist Harold Ridley observed the biocompatibility of PMMA introduced accidentally into pilots' eyes during cockpit canopy explosions, and formed an IOL from the material. It was Dutch and American researchers, however, who developed the concept for practical use.

Early implantations of PMMA IOLs after the removal of the existing natural lens were associated with glaucoma, uveitis and posterior dislocations, and acceptance of the IOL was slow. It was not until 1978, when the advantages of placing the lens in the evacuated capsular bag were recognised, (see box, Capsule filling lens developments for the accommodating IOL) that the use of the IOL for the correction of cataracts was adopted widely. Cataractous lenses could also be removed much more quickly by this time, due to Kelman's phacoemulsification procedure, which uses an ultrasonic 'drill' to break up the lens.

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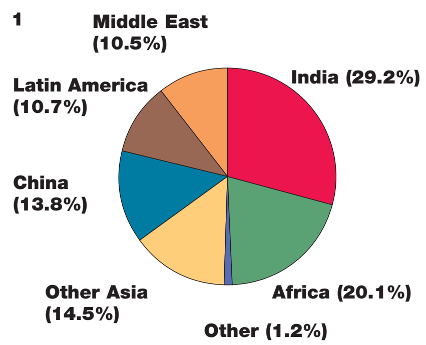

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Lens material	Density g/cm	RI	Transmission %	UTS MPa	El@Break %
(Polymethylmethacrylate)	1.19	1.494	>95	724	2-7
Dimethylsilicone type	0.97	1.408	99	3.5	100
Methylphenylsilicone type	1.05	1.43	98	3.0	200
Copolymer PEA/PEMA	N/A	1.55	>95	1.0-2.3*	200-500*

*Composition dependent – PE(M)A is 2-phenylethyl(meth)acrylate

Blinding divide – global distribution of the 20 millon people blinded by cataracts (WHO 2000), figure 1. Properties of foldable IOL materials, figure 2.

The first generation of lenses were rigid PMMA implants that needed an incision of 5-6mm thick to introduce it into the eye. Reducing surgical eye trauma means a faster recovery for the patient, among other benefits, so the implantation of a foldable IOL in 1986 that halved the effective cross-section and reduced the incision to a self-sealing size as small as 2.65mm prompted a flurry of activity amongst lens manufacturers keen to develop lens designs and new materials suitable for the new foldable lens concept.

The materials most commonly used in the manufacture of foldable IOLs are silicone and hydrophobic or hydrophilic acrylic, figure 2. Acrylic lenses may be lathe-cut from blanks or moulded, wheras silicone IOLs are usually moulded.

Many IOLs developed for posterior placement have an optic of about 6mm in diameter, which has two curved plastic filaments or haptics fixed at diametrically opposite points on the lens circumference. The haptics fix the IOL within the capsular bag, behaving like compressible springs, figure 3. Each haptic extends for an additional 3mm, taking the overall IOL diameter to between 12 and 13mm.

Towards the accommodating IOL

The main goals in IOL research at the moment are to reduce the minimum surgical incision from 2.65mm to 1mm, as well as achieving accommodation in some lens designs. There are reports of accommodating IOLs are being worn successfully by younger patients, so the challenge is to develop an implant that will do the work of the worn-out ciliary muscles in patients who fall mainly in the over 60s age group.

Accommodative claims have been made for a number of conventional IOLs including HumanOptics Akkommodative® 1CU and the AT-45 CrystaLens™. In these pseudoaccomodative designs the haptics are strongly engaged with the capsular bag, and hinge or flex, moving the optic forward in response to the capsular relaxation of accommodation. Measured power increases are about 1.3 Dioptre (D), independent of the basic lens power, and it is suggested that recipients learn to accommodate and their vision improves, progressively.

Another lens design, the ThinOptX®, has been successfully implanted through 1.4mm incisions. It has a convex anterior surface, a diffractive posterior surface, and is 40 microns thick for all powers. The lens bends under ciliary contraction improving near visual acuity.

The recently-reported SmartIOL™, a thermodynamic IOL introduced by Medennium, is a rod of a hydrophobic acrylic polymer gel that can be customised before insertion through a 3mm incision into the evacuated capsular bag. After warming to body temperature, the lens reverts to its premoulded biconvex lens form of about 9.5mm diameter. Medennium claims that the lens accommodates, but computer modelling suggests that the ability of the capsular bag to alter a lenses shape declines sharply with increasing incision diameter.

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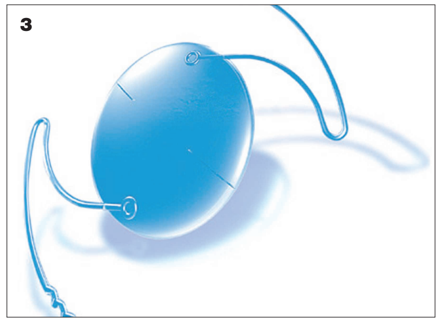

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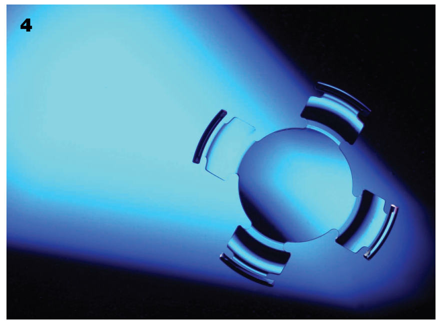

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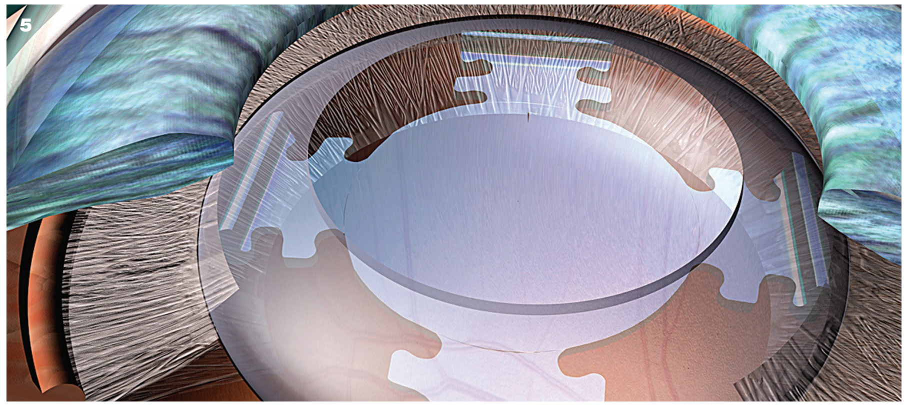

Springy – the Microsil Toric® lens from HumanOptics is a good example of IOLs designed for posterior placement. The springy haptics fix the lens in position within the eye capsule, figure 3. Pseudoaccommodating IOLs currently used include the Akkommodative® 1CU intraocular lens, which is shown prior to implantation, figure 4 and after positioning within the capsular bag. (Images courtesy of HumanOptics AG)

Key dates in intaocular lens development

1795	Casaamata (Germany) attempts implantation of a glass lens.
1949	Ridley (UK) produces a PMMA IOL.
1967	Kelman (US) invents phakoemulsification – ultrasound destruction of a cataract.
1978	Shearing (US) proposes placement of an IOL in the evacuated lens capsule.
1986	Mazzocco (US) patents the foldable IOL.
1997	Staar (US) introduces intraocular contact lenses for myopia and hyperopia.

Opinion is divided on this issue. Eye surgeon I Howard Fine MD was quoted in Cataract and Eye Surgery Today as saying, 'To put the importance of this lens in perspective, if we look at cataract surgery over the last 30 years, there are three major leaps – everything else is an incremental step – Phaco[emulsification] is one, IOLs are the second, and I believe the SmartLens is the third.' There is still a way to go before this lens reaches the market, so time will tell.

None of these lens types appear to demonstrate a reversible addition of 2D – the minimum power increase necessary to correct presbyopia (long-sightedness) in the over-40s. Filling the lens capsule completely via a 1.0mm incision appears to hold the greatest promise in producing an IOL that will retrieve accommodation.

Keeping an eye on the future

The surgery and technology of lens replacement in the human eye has developed rapidly during the past 50 years to the point where the implantation of foldable IOLs for the treatment of cataracts is well established worldwide. New designs of IOL for the treatment of myopia and hyperopia are advancing and are likely to be confirmed within the decade.

Retrieved accommodation in the eyes of non-human primates has been demonstrated using silicone compositions, and the technology of similar injectable systems, able to closely replicate the physical and mechanical characteristics of the young natural lens, is available. So it seems highly probable that ophthalmologists will soon be able to correct not only aphakia but also presbyopia in their older patients.

In vivo capsule filling lens developments in accommodating IOLs

During the past 40 years, many different types of polymer for *in vivo* lens formation have been have been investigated, including silicones, hydrogels, collagen, urethanes and acrylates.

- In 1964, Kessler refilled a rabbit's capsule with silicone elastomer after extracapsular lens extraction. He encountered two problems – removal of the natural lens through a very small incision in the capsular bag, and leakage of injectable materials. The first problem was largely eliminated by phacoemulsification (ultrasonic break-up of the lens).
- Parel used an LTV silicone to reduce leakage into the anterior chamber, but its 24 hour cure time thwarted success. Again, to counteract leakage, Parel and Haefliger injected pre-cured silicone into rabbits' eyes, but pre-curing the elastomer stopped effective moulding of the lens by the capsular bag. A trial using dimethylsilicone polymer implanted into the eye of an old Rhesus monkey was more successful, with the monkey retaining up to 6D of accommodation. A detectable accommodation was also found in a non-human primate following the introduction of an inflatable balloon into the capsule, which was later filled with either silicone oil, or a silicone composition polymerised within two hours. Research was discontinued, probably because lenses were impaired by bubbles and wrinkling.
- In 1994, Hettlich photopolymerised an acrylate monomer by irradiating with blue light (400 to 500nm), using the evacuated capsular bag as a mould to form a lens, and polymerisation was completed within 30 seconds. The technique combined a small incision (1mm) with a command-set system to eliminate leakage. He prepared lenses in vivo in rabbits eyes, and ex vivo in pigs eyes. The system used 2,2'-bis(4-methacryloyl-diethyl-oxyphenyl) propane, in which a bis-acylphosphineoxide blue light photoinitiator, and hydroxymethoxy-benzophenone, a UV absorber, were dissolved. The lenses formed from the resulting polyacrylate (RI 1.53) were too powerful and had too high a Young's modulus to accommodate.
- Hodd, along with co-workers at Pfizer, realised that to simulate the natural lens with a capsule filling lens moulded *in vivo*, it would need to be made from a material with a low injection viscosity, rapid setting of less than minute, a low refractive index and a very low Young's Modulus of less than 6kPa. They proposed injecting an aqueous solution of an acrylated microgel, derived from either N-vinylpyrrolidone/vinyl-alcohol copolymers or poly(N,N-dimethylacrylamide), and a polymeric water-soluble photocrosslinker combining to a macrogel when irradiated with blue light. Unlike linear polymers, microgels exhibit Einsteinian flow in solution, and in the gel do not form phantom crosslinks. The water-soluble photoinitiator, a copolymer of N,N-dimethylacrylamide and 2,4,6-trimethyl-benzoylphenyl-4-vinylphenylphosphine oxide, acted to crosslink the microgel.
- Kreiner adopted similar copolymers for an expansile copolymer lens, where a precisely moulded, dehydrated, hydrogel lens was implanted in the evacuated capsule. Here the lens absorbs water and assumes a full lens form. Both these preceding designs suffer from the high equilibrium water content of vinylpyrrolidone copolymers which generally reduces control of power of the lens.
- Pfizer's silicone gel system, based on a patented invention of Ho, is the most advanced capsule filling, accommodating, lens system. Here a methylperfluoroalkylphenylsilicone tercopolymer is injected through a size 18 cannula, and then crosslinked by conventional platinum/vinyl/hydride chemistry. Refilled cadaver lenses showed an increasing change in lens power regardless of age. With increasing lens diameter, a 59 year old lens and a 32 year old lens had similar diameter:power profiles, implying that if it were refilled with a suitable lens-forming gel and subjected to the same stress, the capsular bag would accommodate, regardless of the age of the patient.

Further reading

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- 'Macromolecular photoinitiator compounds', Inventors: K A Hodd and K A Dillingham, Patent Number: WO 2000055212, Asignee Pharmacia & Upjohn, Groningen B V, Netherlands.
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