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OUTCOME AFTER SURGERY OF CONGENITAL CATARACT

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ABSTRACT

The visual outcome in infants undergoing surgery for bilateral congenital cataract has improved considerably because of improved surgical methods and the realisation that early detection, allowing early cataract extraction and immediate optical correction, can prevent otherwise irreversible deprivation amblyopia.

The management of unilateral congenital cataract is still one of the most difficult problems in paediatric ophthalmology. In unilateral congenital cataract, intervention before six weeks of age has been reported to be optimal to promote visual acuity development. However, in spite of early surgery the results in unilateral cataract have in general been less favourable due to the interocular competition.

Cataract surgery in adults is a safe procedure but complications are more common in children. The aims of the projects were to account for complications and long-term functional results after surgical treatment of children with dense congenital unilateral and dense bilateral congenital cataract operated on before 12 months of age.

Intraocular lens (IOL) implantation in infants might be a better alternative to aphakia. One aim was to study, in an animal model, the effects of IOLs specially designed for the small growing eye.

Complications requiring additional surgery were very common in these infants operated on for congenital cataracts during the first year of life. After-cataract occurred in more than one third of the eyes. Glaucoma requiring trabeculectomy developed particularly in infants who had their cataract extraction very early. Glaucoma development was not more common in infants operated on for after-cataract. The visual outcome was not worse in eyes operated on for after-cataract.

In dense bilateral congenital cataract good postoperative visual acuity was achieved in most healthy children if surgery was performed early, i.e. before 6-8 weeks of age. Chronic glaucoma developed predominantly when the cataract extraction was performed during the first week of life. In dense unilateral cataract a good visual acuity was achieved only in children who underwent cataract surgery early and who adhered to the occlusion therapy schedule. Full compliance to the occlusion therapy programme was uncommon. Chronic secondary glaucoma leading to blindness developed in three out of 12 children operated on within 6 weeks. Persistent foetal vasculature seemed to be a risk factor for secondary glaucoma.

The effects of two types of IOLs designed for small eyes with long haptics forming a ring in the capsular bag were investigated in infant rabbit models and compared to conventional 3-piece AcrySof® IOL and aphakia. The 3-piece AcrySof® IOL was strongly deformed in these small eyes and the vaulting of the lens caused occlusion of the pupil. This lens should probably be avoided in very small eyes. The specially designed IOLs for small eyes did not dislocate but the bulb growth was compromized.

The IOLs reduced or prevented the formation of after-cataract. Considerable after-cataract developed in all aphakic eyes. Glaucoma occurred in pseudophakic eyes as well as in aphakic eyes.

Key words: congenital cataract, cataract surgery, intraocular lens, infant, paediatric, rabbit, complication, glaucoma, after-cataract, posterior capsule opacification.

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LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Lundvall A, Kugelberg U. Outcome after treatment of congenital bilateral cataract. Acta Ophthalmol Scand; accepted.

II. Lundvall A, Kugelberg U. Outcome after treatment of congenital unilateral cataract. Acta Ophthalmol Scand; accepted.

III. Lundvall A, Zetterstrom C. Complications after early surgery for congenital cataracts. Acta Ophthalmol Scand. 1999 Dec;77(6):677-80.

IV. Lundvall A, Kugelberg U, Lundgren B, vd Mooren M, Zetterstrom C. Intraocular lens designed for the newborn infant eye. J Cataract Refract Surg. 2001 Jun;27(6):928-33.

V. Lundvall A, Zetterström C, Lundgren B, Kugelberg U. The effect of 3-piece AcrySof and downsized HSM PMMA intraocular lenses on infant rabbit eyes. J Cataract Refract Surg; accepted.

To my very young patients

Contents

Abbreviations and terms

ANOVA	analysis of variance
Aphakia	absence of eye lens
CF	counting fingers
CI	confidence interval
HM	hand motions
HSM IOL	heparin surface modified intraocular lens
IOL	intraocular lens
IOP	intraocular pressure
PCO	posterior capsule opacification (after-cataract)
PFV	persistent foetal vasculature
PMMA IOL	poly(methyl-methacrylate) IOL
Pseudophakia	natural eye lens substituted with IOL
VA	visual acuity

1. Introduction

Treatment of congenital cataracts remains a challenge; it is resource demanding and difficult. The management requires a dedicated team effort by parents, paediatric ophthalmologist, surgeon, anaesthesiologist, orthoptist and contact lens optician.

1.1. Incidence

Bilateral congenital cataract is the most common cause of treatable childhood blindness. Unilateral congenital cataract is an important cause of amblyopia and strabismus. The incidence of all cases of congenital cataract in western Sweden was reported to be 36 per 100 000 births (Abrahamsson, Magnusson et al. 1999). This incidence is of the same order as that reported from the United Kingdom (Rahi and Dezateaux 2001). The incidence of cases with dense bilateral congenital cataract *operated on* before the age of 1 year in the Stockholm area with a population of about 1.7 million inhabitants during 1992 – 1996 was 12 per 100 000 births. The corresponding figure for cases of unilateral cataract was 8 per 100 000 births.

1.2. Aetiology

In the developed world most cases of bilateral congenital cataracts are idiopathic. About one third are hereditary without systemic disease. These are mostly autosomal dominant but autosomal recessive and X-linked traits occur (Wright, Kolin et al. 1995). Rare causes of childhood cataracts are metabolic disorders such as galactosaemia and hypocalcemia. Many inherited congenital cataracts are combined with systemic abnormalities such as trisomy 21 and Turner´s syndrome. Mental retardation is common in series of bilateral congenital cataract and there is a multitude of inherited syndromes with this combination associated with other abnormalities such as craniofacial or skeletal deformities, myopathy, spasticity or other neurological disturbances (Lambert 1997).

A number of intrauterine infections (toxoplasmosis, rubella, cytomegalic inclusion disease, herpes infection, varicella, and syphilis) may cause congenital cataracts. Of these rubella is the most important (Wright, Kolin et al. 1995). The rubella cataract is usually bilateral but may be unilateral. In Sweden rubella as a cause of eye complications is very rare because of an effective vaccination programme.

Unilateral congenital cataract is as a rule not associated with systemic disease and is seldom inherited. It may be masked bilateral cataract because of asymmetric lens involvement. The majority of cases are idiopathic. About 10 percent are due to lenticonus/lentiglobus and persistent foetal vasculature (Wright, Kolin et al. 1995).

1.3. Morphology

Cataracts are opacities of the crystalline lens and may be subclinical with no or insignificant visual disability. There is a multitude of morphological congenital cataract variants.

Nuclear cataract

Nuclear cataract is usually present at birth and nonprogressive. Dense cataracts present at birth are in most instances of the nuclear type (Parks, Johnson et al. 1993). The opacification is located to the embryonic and foetal nuclei between the anterior and posterior Y sutures and is usually very dense. The eyes are almost always smaller than normal eyes. The cataract is bilateral in about 80 %(Parks, Johnson et al. 1993). In bilateral congenital nuclear cataract inheritance can be demonstrated in 30 – 50 percent. The inheritance is in most cases autosomal dominant.

Posterior cataracts

Posterior unilateral cataracts in infants and children are in most cases caused by persistent foetal vasculature (PFV) - a condition also known as persistent hyperplastic primary vitreous (PHPV) - or posterior lenticonus / lentiglobus (Wright, Kolin et al. 1995).

PFV

Cataract associated with PFV may be present at birth but usually develops later. PFV is a disorder related to the persistence and the secondary fibrosis of the primitive hyaloid vascular system. The cataract is almost always unilateral and the affected eye is usually small. The retrolental vascular structure in contact with the lens capsule may give way to blood vessels encircling the lens causing haemorrhage. The fibrovascular stalk may cause tractional macular detachment. Glaucoma development is common (Lambert 1997).

Lenticonus - lentiglobus

Cataract associated with posterior lenticonus or posterior lentiglobus usually develops after the critical period of visual development (Wright, Kolin et al. 1995). It is largely unilateral and occurs sporadically. It represents the most common type of developmental cataract in normal-sized eyes (Parks, Johnson et al. 1993). The changes in the lens develop as a small defect in the posterior lens capsule, which exhibits a progressive bowing resulting in a posterior bulging and disorganization of the subcapsular lamellae and opacification (Parks, Johnson et al. 1993).

Lamellar cataract

Lamellar cataract usually develops after establishment of fixation. It is usually progressive but may remain subclinical. The cataract involves the lamellae surrounding the foetal nucleus peripheral to the Y sutures (Parks, Johnson et al. 1993). Eyes with lamellar cataracts are usually normal in size with normal-sized cornea. It is uniformly bilateral and autosomal dominant pattern of inheritance is common.

Other morphological cataract types

There are a great number of other - mostly rare - morphological variants of congenital cataracts. Some are due to lenticular developmental defects present at birth. These may have little influence on vision. Such defects are sutural cataract and anterior polar cataract, which usually do not progress. Anterior polar cataract is, however, not infrequently associated with refractive anisometropia and amblyopia. Some children with anterior polar cataract have additional ocular pathology (Jaafar and Robb 1984). Total cataracts involving the whole lens are uncommon. They are classically associated with rubella and are usually bilateral (Parks, Johnson et al. 1993).

1.4. Amblyopia and congenital cataracts

Amblyopia is caused by abnormal structural and functional evolution of the lateral geniculate nucleus and striate cortex due to the abnormal visual stimulation during the sensitive period of visual development.

Reversibility of amblyopia depends on the stage of maturity of the visual system at which abnormal visual experience began, the duration of deprivation and the age at which therapy was instituted. The most critical period is probably between 1 week and 2 months (Wright 1995). Disruption of vision during this period usually causes severe and permanent visual loss. If visual deprivation occurs after the age of 2 – 3 months, the amblyopia is usually reversible. The sensitivity to amblyopia gradually decreases until the age of 6 or 7 years when the visual maturation is complete and the retinocortical pathway and the visual centres become immune to abnormal visual input (von Noorden 1978). It is thus essential that early treatment of dense congenital cataract is instituted in order to avoid irreversible amblyopia.

Visual loss and the development of amblyopia depend on the size and location of the cataract and particularly on the density. If the opacities are large enough to obscure the fundus view through an undilated pupil, amblyopia development can be expected. If retinal details such as the larger vessels can be distinguished through the central portion of the cataract, conservative treatment can be considered. Some infants with partial subclinical congenital cataract develop sufficient binocular interaction and form vision to allow a normal maturity of the visual system. Thus, amblyopia might not be a problem for some children with partial congenital cataract. If surgery is considered in children with partial cataract it should, if possible, be postponed until after one year of age when IOL-implantation is an option and postoperative complications are fewer. Children with partial cataract treated conservatively must be followed closely. Occlusion therapy is necessary in unilateral cases to prevent amblyopia. The clinical evaluation should entail evaluation of visual behaviour including monocular and binocular fixation patterns.

Unilateral congenital cataract, dense from birth, causes amblyopia with loss of binocular function and the development of secondary strabismus. In cases of dense bilateral congenital cataract, bilateral amblyopia and nystagmus will occur. To prevent irreversible amblyopia in infants with dense cataract from birth, the cataract extraction must be performed early.

1.5. Surgery in congenital cataract

Considerable developments in the surgical treatment of cataract in children has taken place since Scheie (Scheie 1960) pleaded for the aspiration procedure in children. Careful and gentle manipulation of the eye at all stages of surgery is important to reduce the breakdown of the blood aqueous barrier (Apple, Solomon et al. 1992) and to reduce inflammation. The lens cortex and nucleus in infants are often soft and can therefore be aspirated (Scheie 1960; Apple, Solomon et al. 1992) so that phacoemulsification methods are unnecessary. By using microsurgical technique small incisions are sufficient for hydrodissection and aspiration/irrigation of the lens. Use of heparin coated IOLs with high biocompatibility reduce the postoperative

reactions. (Percival 1991; Apple, Solomon et al. 1992; Philipson, Fagerholm et al. 1992; Zetterstrom, Lundvall et al. 1992).
By using viscoelastics, the anterior chamber is maintained and the corneal endothelium is protected (Holmberg and Philipson 1984a; Holmberg and Philipson 1984b; Glasser, Osborn et al. 1991). Hydrodissection (Faust 1984; Pandey, Wilson et al. 2001) facilitates the removal of epithelial cells and cortical remnants. Meticulous elimination of the cortex decreases the number of cells that have the potential to proliferate and reduces the risk for a lens-induced inflammation, which might be of importance for the development of complications (Apple, Solomon et al. 1992).
Openings in the anterior and posterior capsule are created with capsulorhexis. The capsulorhexis of the posterior capsule is performed to reduce the problem caused by posterior capsular opacification (after-cataract). Most surgeons prefer the continuous curvilinear capsulorhexis method (Gimbel and Neuhann 1990) in order to minimize trauma. Most surgeons also perform anterior vitrectomy to reduce the after-cataract problem (Cavallaro, Madigan et al. 1998; Ahmadieh and Javadi 2001; Ellis 2002) at least in the youngest (Kugelberg & Zetterström 2002).
The extracapsular aspiration method allows primary or secondary implantation of an intraocular lens. In bilateral cataract only a short interval should elapse between the removal of the lenses to prevent relative amblyopia of the fellow eye (Taylor, Vaegan et al. 1979). In the very young child many surgeons prefer to operate on both eyes in one séance.

1.6. Refractive correction

Postnatal development

The refractory correction of aphakia is complicated in infants because of the rapid changes in the refractory state during childhood. The refractory state is a function of the relation between the axial length and the combined refractive power of cornea and lens. The axial length increases during life from a mean of approximately 16.8 mm at birth to 23.6 mm in adults (Eustis 1995). There is a rapid growth during the first 18 months with an increase in the axial length of about 4 mm (Larsen 1971a; Larsen 1971b; Möller 1997). The axial length then increases 1.1 – 1.2 mm up to the age of 5 years and a further 1.3 – 1.4 mm until the age of 13. The longitudinal growth is minimal after that age. The size of the anterior segment as compared to the adult eye is more developed than the posterior segment in the neonate with diameters that are roughly 75 – 80 percent of the adult eye (Eustis 1995).The horizontal corneal diameter in the newborn averages 9.8 mm (Blomdahl 1979). The corneal changes during the first year of life include thinning, flattening and enlargement. The diameter increases to 11 – 12 mm during the first year of life. The mean refractive power of the cornea decreases from about 51 diopters at birth to 45 diopters at 6 months of age and to 43.5 diopters in adults (Gordon and Donzis 1985).
The lens growth is also rapid during the first year of life. The diameter at birth is (Bluestein, Wilson et al. 1996) approximately 6.0 mm and increases to about 7.7 mm at 6 to 9 months and to about 9.3 mm at 16 years. The refractive power of the lens decreases from 34.4 to 18.8 diopters (Gordon and Donzis 1985). The diameter of the postlensectomy capsular bag is 1 mm larger. The capsular bag growth does not

continue after lensectomy, which is of importance when selecting lens implant (Wilson, Apple et al. 1994).

Contact lenses

To avoid amblyopia the induced aphakia must be optically corrected as soon as possible after surgery. Contact lenses are the standard method in small children and, ideally, the lenses are fitted in the operating room. Some authors recommend an extended wear lens regimen during the first year of life in order to ensure a clear retinal image at all times (Wright, Kolin et al. 1995). To reduce the risk for contact lens complications, many prefer to remove the lenses at night (Schein, Glynn et al. 1989; Lambert 1997).

Several types of lenses are available. Rigid gas permeable lenses have a wide range of available powers and have great ability to correct large astigmatic errors. They are easy to insert and to remove (Amos, Lambert et al. 1992) but cause more foreign body sensation than soft lenses. The two major soft lens types are silicone and soft hydrogel lenses. Both are suitable but soft hydrogel lenses are less expensive which is an important consideration due to frequent lens loss. Loss of lenses and the growth of the eye during infancy necessitate frequent lens replacements especially during the first 2 years of life. A lost lens must be replaced immediately so that parents should have at least one back-up lens in reserve. Frequent retinoscopy must be performed to decide the power of the lens. The normal lens power decrease from birth to 1 year of age is approximately 10 diopters. Most authorities recommend an overcorrection of +2.0 – +3.0 D until bifocals can be tolerated from the age of 2 – 4 years. Optimal fitting of the lens is important. The lens must be removed if local irritation with inflammation and discharge occur. Otherwise serious complications such as ulcerative keratitis and corneal scarring may follow. These problems are more common in small infants who wear the lenses overnight.

Complications due to hypoxia such as corneal oedema and superficial circumlimbal vascularization, may occur so that close supervision is important.

A good compliance with wearing contact lens demands close cooperation with the parents. In less than 10 percent of infants, contact lenses cannot be used because of complications (Amaya, Speedwell et al. 1990). Nevertheless, periods of uncorrected aphakia are common in infants. The child should be provided with aphakic spectacles as an option if contact lenses are unsuitable.

Intraocular lenses (IOL)

In adults the introduction of intraocular lenses (IOL) implants is epoch-making. With the introduction of viscoelastics, improved surgical technique and modern posterior chamber lens implants, IOLs are being implanted also in children. Capsular fixation is preferred over ciliary sulcus placement because such complications as pupillary capture and IOL descentration are more common with ciliary sulcus fixation (Pandey, Wilson et al. 2001). Furthermore, intracapsular IOL reduces after-cataract formation (Zetterström, Kugelberg et al. 1996). Many problems concerning the refractive correction would be solved if IOL could be implanted in neonates. The use of IOL in infants is, however, controversial because of the smallness of the eye and the very rapid eye growth in the first years of life. Another disadvantage with IOL implantation in infants is the difficulty in predicting refraction. Thus, today IOL is not

usually recommended in children until the age of 1 to 2 years or older. In children 2 to 3 years of age, an IOL refractive power dimensioned for emmetropia implies a mild myopia (approximately −2.0) in adulthood. If an IOL is implanted in the newborn, the rapid axial growth during the first 2 years of life must be taken into consideration, which means that the IOL has to be combined with a contact lens during these first years.

Available IOLs are dimensioned for the adult eye and have refractions adapted to the adult eye. In animal experiments oversized implants retard the eye growth (Kugelberg, Zetterstrom et al. 1997b) and may cause complications such as degenerative changes in the peripheral retina and neovascularization of the ciliary body (Kugelberg, Zetterstrom et al. 1997a). Adult-size IOLs may cause marked ovalization of the capsular bag (Pandey, Wilson et al. 2001). Microcornea and/or microphthalmos, common in congenital cataracts, add to the IOL sizing problem. The need for a smaller IOL designed for infants has been recognized by several authors (Dahan and Drusedau 1997; Lambert, Buckley et al. 1999).

The inflammatory response in small children is greater than in older children (Apple, Solomon et al. 1992). It is partly related to the type of IOL. Thus, a reduced inflammatory response has been observed with heparin surface modified IOL implants (Percival 1991; Philipson, Fagerholm et al. 1992; Zetterstrom, Lundvall et al. 1992).

Apart from avoiding the need for secondary IOL implantation, a primary implantation in the capsular bag in the newborn would decrease the after-cataract formation. Glaucoma development is common in infants who undergo cataract extraction without IOL. It has been suggested that IOL implantation might reduce the incidence of glaucoma in children (Asrani S 2000). A multicentre study (the Infant Aphakia Treatment Study) (Lambert, Buckley et al. 1999) has been started in the USA to evaluate IOL implantation versus contact lens correction for infantile aphakia.

The ideal IOL designed for the newborn should have such properties that it prevents after-cataract formation, minimizes the inflammatory response, and minimizes uveal lesions and glaucoma development.

One aim of the present study is to test whether downsized IOLs might be suitable for small eyes (papers IV and V)

1.7. Occlusion therapy

Providing a clear image by removing the cataract and refractory correction of aphakia is not sufficient to cure amblyopia if ocular dominance is present. Ocular dominance is diagnosed by careful analysis of fixation behaviour. If amblyopia is suspected, occlusion therapy of the preferred eye should be initiated. Patching is always necessary after surgery of congenital unilateral cataract. The problem of optimal occlusion time in unilateral cataract is controversial. According to animal experiments (von Noorden 1977) and clinical experience (Jeffrey, Birch et al. 2001), visual acuity does not develop in amblyopia if there is insufficient occlusion. On the other hand, too intensive patching prevents the development of binocular function. Most authors recommend patching of the phakic eye during 80 % of waking time or more, at least during the first months of life (Beller, Hoyt et al. 1981; Robb, Mayer et

al. 1987; Birch and Stager 1988; Drummond, Scott et al. 1989; Cheng, Hiles et al. 1991; Birch and Stager 1996). Brown et al (Brown, Archer et al. 1999) used a reduced occlusion schedule consisting of one hour per day per month of age for the first 6 months of life and the occlusion did not exceed 50 %. In a study by Jeffrey et al (Jeffrey, Birch et al. 2001) there was no difference in visual acuity between an intensive occlusion group patched 80 % of waking hours and a reduced occlusion group patched 25 – 50 % of waking hours. They suggested that a reduced occlusion may be associated with better binocular sensory outcomes and a reduced prevalence of strabismus without compromising good visual acuity in children treated for congenital unilateral cataract.

1.8. VA results

With improved surgical techniques, immediate optical correction and the timing of surgery with regard to the risk for amblyopia development, the VA results have improved considerably at least in bilateral congenital cataract. In unilateral cataract the VA results have been less favourable. The aphakic eye cannot accommodate so that it loses in the binocular competition with the intact eye. According to Helveston et al (Helveston, Saunders et al. 1980) "there is virtually no chance of achieving a good visual result despite early surgery, prompt aphakic correction, and aggressive amblyopia therapy" in congenital unilateral cataract. However, in selected small series good VA development has been reported.

For many reasons there are great difficulties in comparing the results of congenital cataract treatment of different published series. Most series are selected; the results are much better when children with co-morbidity are excluded. With the inclusion of children with partial progressive cataracts, better visual results can be expected. In cataracts allowing clear images during the period with the highest sensitivity to visual deprivation, the risk for amblyopia is much lower than in infants with dense cataracts from birth. Most reports concern older children. The published unselected series of dense cataracts operated on before the age of one year are small and often selected.

One aim of the present investigation is to account for the functional results of cataract surgery in series of consecutive and unselected cases of dense bilateral and unilateral cataracts operated on before the age of 12months (papers I and II).

1.9. Surgical complications

Surgical complications are more common in infants than in older children (Keech, Tongue et al. 1989). Early surgical complications after cataract extraction include acute pupillary block glaucoma, retinal haemorrhages, wound leak, synechiae of iris to the wound, vitreous leakage to the incision and endophthalmitis. Apart from acute pupillary block glaucoma, such complications are very uncommon. After IOL implantation, postoperative anterior uveitis is a common complication (Pandey, Wilson et al. 2001). Topical steroids are used to reduce the postoperative inflammatory response. Intraocular fibrinolytic agents have been used to dissolve fibrinous exsudates.

Long-term complications may cause serious problems. It is important to diagnose and treat complications such as after-cataract and secondary glaucoma as soon as possible

to avoid deprivation amblyopia or damage of the optic nerve. Frequent checks are necessary especially during the first year.

After-cataract

After-cataract (also referred to as posterior capsule opacification PCO) occurs in nearly all infants with intact posterior capsule (Nishi 1986; Apple, Solomon et al. 1992) and is a common cause of decreased visual acuity requiring secondary intervention. It is largely due to proliferation of anterior lens epithelial cells (McDonnell, Zarbin et al. 1983; Apple, Solomon et al. 1992). Lens epithelial cells migrate from the periphery to the posterior capsule and may form a ring in the retroiridal space – known as Soemmerrings´s ring (Kappelhof, Vrensen et al. 1985; Taylor 1997). This process might possibly be of importance in the development of a more serious complication, i.e. chronic glaucoma, by affecting the chamber angle and the trabecular meshwork. The posterior capsule opacification can also occur as pearls spread on the posterior capsule known as Elshnig´s pearls (McDonnell, Zarbin et al. 1983). Metaplasia of anterior lens epithelial cells can cause fibrosis, wrinkles and contracture of the capsule. After-cataract formation is much more pronounced in infants than in adults (Apple, Solomon et al. 1992).

The problem of blockage of the visual axis by after-cataract can be reduced by posterior capsulorhexis and anterior vitrectomy (Vasavada and Desai 1997; Pandey, Wilson et al. 2001; Hosal and Biglan 2002).

In humans and in animal experiments after-cataract development is reduced following intraocular lens implantation. The after-cataract formation after IOL implantation is influenced by the surgical technique (Hollick, Spalton et al. 1999) as well as the composition (Hollick, Spalton et al. 1999), compressibility, size (Meacock, Spalton et al. 2001a,b), capsular bag implantation or sulcus fixation (Laurell, Zetterstrom et al. 1998) and the form of the IOL (Nishi, Nishi et al. 1998). In newborn rabbit eyes, the after-cataract formation was reduced with a 10 mm tension ring but not with a 7 mm tension ring (Kugelberg, Zetterstrom et al. 1997a). Hydrodissection and irrigation might be important to wash away epithelial cells (McDonnell, Zarbin et al. 1983).

Cytostatic drugs such as fluorouracil (Kugelberg, Lundvall et al. 2000) colchicine (Legler, Apple et al. 1993) and daunorubicin (Hartmann, Wiedemann et al. 1990) have also been used experimentally to inhibit epithelial cell proliferation.

Glaucoma

Glaucoma is a common complication, the incidence varying from 3 to 32 percent (Asrani and Wilensky 1995; Pandey, Wilson et al. 2001) Glaucoma occurring soon after surgery is in most cases due to pupillary block. Both chronic open-angle and chronic closed-angle glaucoma occur after surgery for congenital cataracts (Phelps and Arafat 1977; Keech, Tongue et al. 1989; Simon, Mehta et al. 1991; Mills and Robb 1994). Chronic closed angle glaucoma is probably caused by peripheral anterior synechiae (Simon, Mehta et al. 1991; Asrani and Wilensky 1995; Johnson and Keech 1996). Open angle glaucoma can develop many years, even decades after the cataract surgery so that the patients have to be followed throughout their lives (Asrani and Wilensky 1995).

Other complications

With modern surgical techniques and the extracapsular cataract extraction, early complications such as cystoid macular oedema, endophthalmitis, and early retinal detachment are uncommon. However, retinal detachment can occur after many years (McLeod 1986; Francis, Ionides et al. 2001).

The published experiences of complications in infants, cataract extracted during the first year of life, are limited.

One aim of the present study is to account for complications in an unselected series of consecutive congenital cataracts operated on before the age of 12 months (paper III).

2. Aims of the present study

Early surgery is necessary to attain useful visual acuity results in dense congenital cataract. It is a common conception that complications are more frequent in newborn infants. The published experiences of surgery for dense congenital cataracts diagnosed and operated on during the first year of life in an unselected material are limited. Intraocular lens implantation in newborn infants might be an option if suitable lenses for small eyes were available.

Main aims of the present study were:

To evaluate the long-term functional outcome after early treatment of congenital bilateral and unilateral cataract (I, II).

To study the type and frequency of complications requiring additional surgery in infants operated on for congenital cataract before 12 months of age (III).

To study the occurrence of complications in relation to age at primary surgery (III).

To evaluate IOLs specially designed for small eyes in animal experiments (IV, V).

3. Material and Methods

3.1. Studies on humans

3.1.1. Outcome after treatment of congenital bilateral cataract

In paper I a retrospective review was undertaken of the medical records of 32 consecutive infants who underwent surgery for bilateral dense cataract before 12 months of age at St. Erik's Eye Hospital during the five-year period from October 1991 to August 1996. Six infants were excluded because of severe general malformations or death before two years of age (5 infants). Three children were excluded because of the cataract being developmental – they had a normal fixation pattern during the first months of life. One was excluded because of missing records. The records of 22 patients, 12 girls and 10 boys, were studied. Children operated on during the first two to three weeks of life were diagnosed at obstetric clinics taking part in a screening programme.

In six children the cataract was dominantly inherited. Seven children had marked bilateral microphthalmos. Nineteen out of 22 children had nuclear cataracts. The cataracts of three infants were not described in the records.

Apart from one child with very low birth weight, pregnancies had been uncomplicated.

In 13 infants with congenital cataract no associated systemic or other ocular abnormality except for bilateral microphthalmos (four children) was present.

Nine patients had associated systemic or ocular abnormalities. All but one were mentally retarded implying difficulties concerning postoperative treatment and less reliable VA measurements. Two of them had Down's syndrome and one Lowe's syndrome. One mentally retarded child had a very low birth weight, 1100 g. The child, who was not mentally retarded, had retinal dysplasia. Three children in this group had microphthalmos.

Indication for surgery was opacities large enough to obscure the fundus view through an undilated pupil. The surgical technique of the cataract extraction was the same in all operations. Both eyes were operated on simultaneously. The surgery consisted of anterior capsulorhexis, aspiration/irrigation of the nucleus and cortex, posterior capsulorhexis, together with anterior vitrectomy and peripheral iridectomy. Extended wear hydrogel contact lenses were fitted directly after the operation was completed. The age of the child decided the dioptre of the first contact lenses, following a schedule with correction for near vision; a newborn child was given +37 dioptres. The contact lenses were worn on an extended-wear basis for the first few weeks and thereafter in daytime. Dexamethasone 1 mg/ml topically was given 3 times a day during one week, twice a day during 2 weeks and once a day during one week. Tropicamide 5mg/ml 3 times daily was administered for 2 weeks. The children were checked weekly for one month and then every 4 – 6 weeks during the first year, thereafter every third month. They were checked by a team consisting of a paediatric ophthalmologist, a contact lens optician and an orthoptist. Retinoscopy was performed on each check to decide the power of the lens. They were provided with aphakic spectacles in case of contact lens problems. At 2 to 3 years of age, the

children were fitted with contact lenses for distance vision and bifocal spectacles for near vision. The postoperative follow-up period included the most recent examination of each patient. During the first years most of the children were followed up at St. Erik's Eye Hospital and then about 50 per cent of the children were checked at their home clinics.
The patients were followed up to 4 – 9 years of age. Visual acuities were recorded using Snellen linear letters or LH linear symbols. Stereopsis was tested with Lang 1 Stereo test (550 seconds of arc). In some cases the patient was severely mentally retarded and the visual acuity determination could not be performed. Records were reviewed to identify patients with nystagmus, strabismus, and postoperative complications.

3.1.2. Outcome after treatment of congenital unilateral cataract

In paper II a retrospective review was undertaken of the medical records of 31 infants (17 girls and 14 boys) who underwent surgery for unilateral congenital cataract before 12 months of age at St. Erik's Eye Hospital during the 5-year period from October 1991 to August 1996. The series is consecutive, one girl was excluded as she developed cataract on the fellow eye. Children operated on during the first 2 to 3 weeks of life were diagnosed at obstetric clinics taking part in a screening programme. In 16 cases the cataract was right-sided and in 14 cases left-sided. One child was mentally retarded. Six patients showed evidence of persistent foetal vasculature (PFV). Severe microphthalmos was present in 4 children. Otherwise, no child had developmental defects. Three patients were born prematurely (in week 27, 35 and 36 respectively). One mother had diabetes mellitus during pregnancy and one mother had pregnancy toxicosis. Otherwise, pregnancies had been uncomplicated.
Indication for surgery was opacities large enough to obscure the fundus view through an undilated pupil. Sixteen had nuclear cataracts, six PFV, one posterior subcapsular cataract, one anterior polar with pupillary membrane and one had lamellar cataract. Four cataracts were not described in the records.
Concerning surgical technique and postoperative treatment see 3. 1. 1.
Patching was initiated as soon as the operated eye had clear media and 50 to 75 percent of waking time was prescribed. This was then modified on an individual basis, according to fixation preference, and interocular differences quantified by clinical preferential looking grating acuity (Teller acuity cards). According to the present schedule, occlusion therapy up to the age of 6 – 7 years is planned. At 2 to 3 years of age, the children with a useful visual acuity were fitted with contact lenses for distance vision and bifocal spectacles for near vision.
The postoperative follow-up period accounted for in this study included the latest examination of each patient. During the first years most of the children were followed up at St. Erik's Eye Hospital and then about 50 per cent of the children were checked at their home clinics.
The patients were followed-up to 4 – 9.5 years of age. Linear Snellen visual acuity at last check is accounted for. The records were reviewed to identify patients with nystagmus, strabismus, after-cataract and glaucoma. The period of occlusion therapy and patching compliance are also accounted for.

Seven children with unsatisfactory VA development and contact lens difficulties had secondary intraocular lens implantation after the age of one year. Primary IOL implantation was performed in the 2 oldest infants (11 months of age).

3.1.3. Follow-up of complications requiring additional surgery in children operated on for congenital cataract before 12 months of age

In paper III a retrospective review was undertaken of the medical records of all infants who underwent surgery for congenital cataract before 12 months of age at St. Erik's Eye Hospital during the five-year period from October 1991 to August 1996 in order to identify any post-operative complication requiring additional surgery.
Sixty-three infants were operated on for congenital cataracts during the period. Thirty-two patients had bilateral and 31 had unilateral cataract. Seventy-five percent of the operations were performed by the same surgeon, the remaining twenty-five percent by three other different surgeons. Six infants with bilateral cataracts were excluded because of severe general malformations or death prior to two years of age (five infants). In all, 57 infants with 83 operated eyes remained. The median age at surgery was 9 weeks (range 4 days to 12 months). The postoperative follow-up period reported in this study included the most recent examination of each patient. Most infants were followed up at St. Erik's Eye Hospital. A few were checked at their home clinic. The postoperative follow-up period ranged from 9 to 70 months (median 32 months).
The intraocular pressure (IOP) was not measured routinely as this requires general anaesthesia in small infants. Parents were told to contact the hospital if any eye problem were to arise, such as teary eye, growing eye or photophobia.
The glaucoma diagnosis was based on clinical signs: epithelial oedema, dark red reflex, photophobia and fast regression of hyperopia or growing eye. The IOP was determined in ketamine hydrochloride anaesthesia when any of these signs was present. After-cataracts and secondary membranes were operated if there was any significant disturbance of the visual axis.

3.2. Studies on rabbits

In papers IV and V, an experimental albino infant rabbit model (New Zealand White) was used. The lens size of the newborn infant (the mean diameter at birth and at 6 to 9 months is 6.0 and 7.7 mm, respectively, (Bluestein, Wilson et al. 1996) is of the same order as the lens size (about 7.5 mm) of the 3-week-old rabbit. However, the ocular axial length of the 3-week-old rabbit is shorter (12 - 13 mm) than that of the newborn infant (16.2 mm) (Isenberg, Neumann et al. 1995). Measurements were performed before surgery and each month up to 6 months after surgery in paper IV, and up to 3 months in paper V.

3.2.1. The surgical procedure

Three-week-old rabbits were anaesthetized with 0.2 mL ketamine hydrochloride (50 mg/mL Ketalar®) and 0.1 mL xylazine chloride (20 mg/mL Rompun®). Topically applied tetracaine chloride (Tetracaine®) was used for local anaesthesia, and pupils

were dilated with a combination of cyclopentolate 0.75% and phenylephrine 2.5%. The surgery was performed by one experienced anterior segment surgeon (C.Z.) and was standardized as much as possible.

A 3.0 mm corneal incision was made. After injection of sodium hyaluronate (23 mg/mL Healon GV®), a continuous capsular opening was created. The nucleus was hydrodissected, and aspiration/irrigation of the nucleus and cortex was performed in the posterior chamber using balanced salt solution (BSS®) containing heparin (Heparin Sodium Injection, USP; 0.75 mL of 1000 U/mL). The corneal incision was closed by a continuous 10-0 nylon suture. A standard dose of dexamethasone (1 mg/mL) was administered 3 times daily and tropicamide 5 mg/mL twice daily in both eyes during the first postoperative week.

In paper IV, a custom-made (Pharmacia & Upjohn) downsized single-piece biconvex heparin surface modified polymethyl methacrylate (HSM-PMMA) IOL with long loops was implanted in the capsular bag in one eye selected at random.

In paper V, the animals were divided into two groups. In group 1, a custom-made (Pharmacia & Upjohn) downsized HSM PMMA IOL with long loops was implanted in the capsular bag in one randomly selected eye after the incision had been enlarged to 5.0 mm, the other eye was left aphakic. In group 2, a 3-piece Acrysof® IOL (MA 30 BA from Alcon, with optic size 5.5 mm and length 12.5 mm) was implanted in one randomly selected eye after the incision had been enlarged to 3.4 mm. The other eye was left aphakic.

3.2.2. Ultrasound measurements

In papers IV and V, ocular axial length was measured using a Sonomed A-scan A 1500 fitted with a short focal length crystal and modified software. The average of several consecutive measurements from each eye was used as the true value of the axial length (Butcher and O'Brien 1991).The measurements were performed using local anaesthesia (topically applied tetracain chloride). The sound velocity in the phakic and aphakic eyes was 1548 m/sec and 1532 m/sec respectively. If the eye was implanted with an IOL the values were corrected according to the formula $V = \frac{AL}{\frac{C}{V_C} + \frac{L}{V_L} + \frac{AL - C - L}{V_{A/V}}}$ where C= corneal thickness, L= IOL thickness, V_C= sound velocity in cornea, V_L= sound velocity of the IOL and $V_{A/V}$= sound velocity in the aqueous/vitreous. The calculated velocities at each timepoint were then used in the formula $AL_{corr} = AL \times \frac{V}{1.532}$ (Hoffer 1994).

3.2.3. Corneal diameter

Corneal diameter was measured horizontally and vertically using a pair of compasses. There was no difference between the two values.

3.2.4. Corneal thickness

The corneal thickness was measured using a Storz Omega Pachymeter. All measurements were performed using local anaesthesia (topically applied tetracain chloride).

3.2.5. Intraocular pressure

In paper IV, after topical instillation of tetracain chloride, the intraocular pressure (IOP) was measured with a pneumatonometer (Mentor Model 30 Classic Pneumatonometer Mentor O & O, Inc. Norwell MA). In paper V, the IOP was measured after instillation of lidocain-fluorescein using a handheld Perkins tonometer.

3.2.6. After-cataract

When the measurements were completed, the rabbits were sacrificed and the eyes were enucleated. Each enucleated globe was sectioned in the coronal plane just anterior to the equator. The after-cataract was carefully removed and weighed to the nearest mg to determine the wet mass (Lundgren, Jonsson et al. 1992).

3.3. Compression tests of different implants

In paper V, a compression test of a downsized heparin-surface-modified poly(methyl methacrylate) (HSM PMMA) intraocular lens (IOL) with long haptics and a 3-piece Acrysof® IOL was carried out. The implant was placed uncompressed between two anvils, and (optic with haptics) was then compressed to 7.5 mm. The capsular bag in 3-week-old rabbits is approximately 7.5 mm.

3.4. Statistical methods

In paper IV, analysis of differences between paired observations was made with the paired *t*-test. Linear regression was employed for analysis of differences in axial growth.

In paper V, statistical analyses were made using two-way analysis of variance (ANOVA) and Wilcoxon rank-sum and signed-rank test.

4. Results and Discussion

4.1. Studies on humans

4.1.1. Functional results in children operated for congenital bilateral cataract before 12 months of age (Paper I)

In the present study all consecutive children with bilateral congenital cataract who underwent surgery before the age of 12 months during a five-year period were included, with the exception of one infant with severe general malformations or those who died before the age of 2 years (five patients). Children with developmental cataract who had a normal fixation pattern during the first months of life were also excluded (three patients).

The functional results in this "unselected" series of the 44 eyes of 22 children at follow-up periods of between 4 to 9 years after the surgery were unsatisfactory in many children (Figure 1). The median VA of the 44 eyes was 0.16. The corresponding figure of the better eye was 0.3. Five children had a VA of the better eye of less than 0.1.

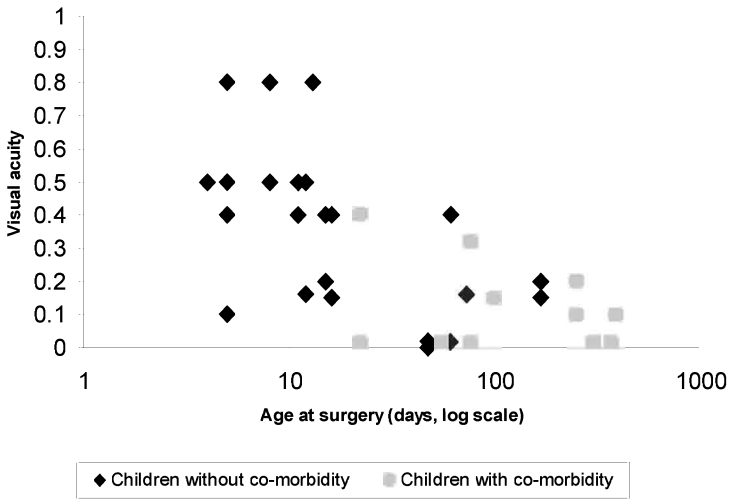

Figure 1. VA of all eyes after surgery (three patients with co-morbidity excluded in whom VA could not be measured).

The results highlight the importance of selection when it comes to comparing the results of different series. Thus, if children without systemic or coexisting ocular morbidity are selected, the functional results are much better. In this group of 13 children, the median VA of all 26 eyes was 0.4 and the median VA of the best eye of the 13 children was 0.4 – 0.5 (Figure 2). As six of the children were below the age of 7 years their VA can be expected to improve (Brown and Yamamoto 1986).

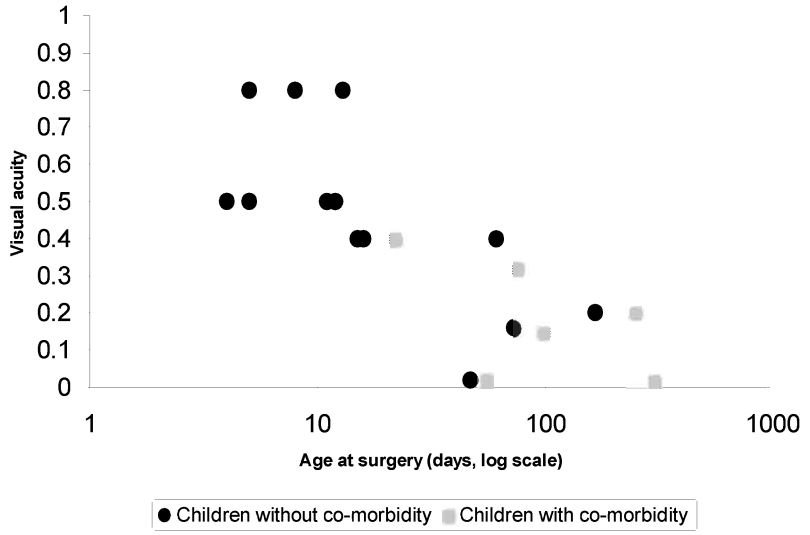

Figure 2. VA in the better eye after surgery (three patients with co-morbidity excluded in whom VA could not be measured).

As in other reports (Bradford, Keech et al. 1994; Spierer, Desatnik et al. 1998), the functional results in children with mental retardation or other contributing systemic and ocular abnormalities were poor. The median VA in nine such children was less than 0.1. Only four out of 18 eyes attained a VA better than 0.1 (Figure 1). In mentally retarded children the postoperative care is difficult to optimise and reliable VA determinations are difficult to obtain. Another cause of low VA might be cerebral visual impairment in mentally retarded children. In the eight children with mental retardation in whom reliable VA could be estimated, only two reached a VA above 0.3 (0.4 and 0.32 respectively) in the better eye (Figure 2).

In the 13 children who *did not* have systemic or coexisting ocular abnormality (except for microphthalmos), nine were operated on within the first 16 days of life. They obtained a VA of 0.4 – 0.8 in the better eye (Figure 2). Four of the 13 children developed stereopsis; all four had undergone surgery within the first 2 weeks of life. One child cataract extracted at the age of 7 weeks showed intense inflammatory reactions with early after-cataract formation and glaucoma development. One eye was blind and the other had a VA of counting fingers (CF). One child cataract extracted at the age of 2 months had a VA of 0.4 in the better eye but a VA of CF in the other eye because of contact lens problems and keratitis. Two children in this group of 13 underwent cataract extraction after the age of 2 months. They obtained a VA of 0.15 –0.16 in the better eye.

The results accord with those given in other reports (Taylor, Vaegan et al. 1979; Jacobson, Mohindra et al. 1981; Rogers, Tishler et al. 1981; Gelbart, Hoyt et al. 1982; Parks 1982; Kugelberg 1992), emphasizing the importance of early surgery to achieve a good VA in dense congenital cataracts. The critical period during which visual

deprivation causes irreversible amblyopia in humans is usually considered to be the first 2 or 3 months of life if the cataract is dense from birth. If a good VA is obtained following cataract surgery after 2 – 3 months of age, the cataract was probably partial during the critical period (Gelbart, Hoyt et al. 1982).

The results in the children of the present series who do not have associated systemic or ocular abnormality except for microphthalmos and who are operated on within one year of age are comparable with other likewise selected series (Table 1).

Study	Age at surgery	No. of children	Visual acuity
Rogers, Tishler et al. 1981	< 6 months	7	"Normal" in 3 operated before 8 weeks, visual lag in 4 operated after 10 weeks
Gelbart, Hoyt et al. 1982	< 42 weeks	24	29/48 eyes VA 20/60 or better; 13/48 eyes 6/60 or worse
	> 2 months	7	6/7 patients 6/60 or worse
Hing, Speedwell et al. 1990	< 1 year	26	14/26 children > 6/24 or better in the better eye
	< 2 months	6	5/6 children > 6/24 in the better eye
Robb and Petersen 1992	< 1 year	24	Median of the better eye 20/63, range 20/30 - 20/100
Kugelberg 1992	< 60 days	7	Median of binocular vision 20/80, range 20/100 - 20/20
Bradford, Keech et al. 1994	< 2 months	16	Median of the better eye 20/50, range 20/200 - 20/20
Lundvall & Kugelberg 2002	< 12 months	13	Median of all eyes 0.4 (range amaurosis - 0.8)
	< 3 weeks	9	Median of all eyes 0.4 - 0.8 (range 0.15 - 0.8), median of the better eye 0.5 (range 0.4 - 0.8)

Table 1. Age at surgery and visual results in children without associated systemic or ocular abnormalities.

Stereopsis was achieved in four children who where orthophoric and never needed occlusion therapy. The cataracts of these infants were extracted within 3 weeks of age and with good visual results bilaterally. In humans the critical period concerning the development of motor fusion is probably the first 2 – 4 months of life (Birch, Shimojo et al. 1985; Mohindra, Zwaan et al. 1985; Archer, Sondhi et al. 1989). According to animal studies, the normal development of binocular cortical cells requires clear and equal retinal images (Wiesel and Hubel 1963; von Noorden and Crawford 1977; Ikeda and Tremain 1978; Hendrickson, Movshon et al. 1987) during the critical period of visual development.

The present results and results in comparable series indicate that in bilateral dense congenital cataract in children without co-morbidity, cataract treatment with the present technique within the first weeks of life can be expected to give a VA of 0.4 to 1.0 in the better eye but vision threatening complications might occur.

Complications are discussed in Paper III.

4.1.2. Functional results in children operated for congenital unilateral cataract before 12 months of age (Paper II)

In this report all 30 infants are included who underwent surgery at St. Erik's Eye Hospital during a 5-year period for unilateral congenital cataract before 12 months of age. The median age at follow-up was 6 years and the visual results are shown in Figure 3.

Six out of 30 achieved a VA of 0.1 – 0.4 in the aphakic eye. All of these children were operated on within the age of 3 months. Seventeen of them attained a VA of counting fingers (CF) at a distance of 0.5 – 1 meter and one a VA of perception of hand movements. In the remaining seven aphakic eyes there was at best light perception, and three eyes were amaurotic. None of the 10 infants who underwent surgery after the age of 3 months reached a VA better than CF at a distance of 0.5 - 1 meter.

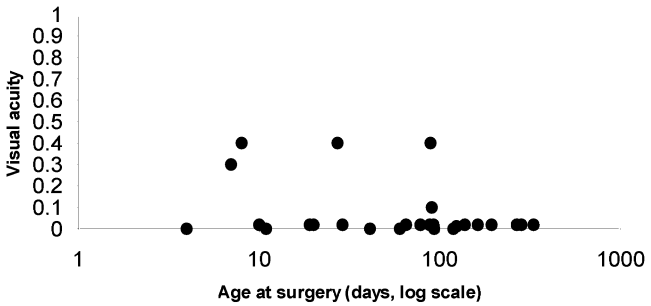

Figure 3. VA after surgery in unilateral cataract.

All 30 patients had strabismus, and seven of them had nystagmus on the aphakic eye. Others have reported similar disappointing results. Helveston (Helveston, Saunders et al. 1980) considered that in unilateral congenital cataract "there is virtually no chance of achieving a good visual result despite early surgery, prompt aphakic correction, and aggressive amblyopia therapy". Some authors have reported better visual outcome (Beller, Hoyt et al. 1981; Birch, Swanson et al. 1993; Birch and Stager 1996; Jeffrey, Birch et al. 2001) and even the development of stereoacuity (Wright, Matsumoto et al. 1992; Brown, Archer et al. 1999; Jeffrey, Birch et al. 2001). Most of these series have, however, been strongly selected. The present series is an unselected material of children operated on for dense unilateral congenital cataract before 12 months of age including subjects with PFV and microphthalmos as well as subjects with poor patching compliance and children developing complications. When including only the children who were operated on by the age of 6 weeks, and excluding those with PFV, severe microphthalmos and severe secondary glaucoma, four out of five patients reached a VA of 0.3 and 0.4.

Our results in this unselected series are in accordance with experiences reported by Wilson and Lambert in a panel discussion in 1999 (Buckley, Lambert et al. 1999). Wilson stated that "we all remember our one success but the average is probably closer to 20/100 or 20/200, even with an enormous amount of effort". Lambert referred to visual acuity data collected from a group of paediatric ophthalmologists concerning paediatric materials with contact lens correction after cataract surgery, and found that only about 20% of the children with unilateral cataracts ended up seeing 20/40 or better, and about half the children had a VA of 20/200 or worse in their aphakic eyes.

One infant operated on at the age of 3 months attained a VA of 0.4. Her cataract was of the lamellar type and might have been progressive which could explain the good visual result in spite of late surgery.

Of the nine children operated on after the age of three months none obtained a vision better than CF. This accords with animal experiments showing that visual deprivation during the sensitive period causes irreversible neurological changes in the visual system (Hubel and Wiesel 1970; Hendrickson, Movshon et al. 1987) and clinical experiences in infants (Birch and Stager 1996). Besides early surgery, another condition of favourable visual acuity development is the absence of vision threatening complications such as glaucoma. Of 13 infants operated on within 2 months of age, four obtained a vision of 0.3 – 0.4. The other nine obtained a VA below 0.1. The low VA was due to severe glaucoma in four infants.

Optimal refractory correction and occlusion therapy are other prerequisites for favourable visual rehabilitation. Most children accepted the contact lenses but lens intolerance probably explained a low VA in one child who underwent surgery within the first week of life.

Although the question of optimal occlusion time is controversial, it is obvious that the occlusion therapy was insufficient in many children. On the whole, patching was problematic. Some infants refused patching and some parents gave up when they found that it distressed the child. Only five children are proceeding with the occlusion therapy according to our schedule, four of them have a VA of 0.3 – 0.4 and the fifth has a VA of 0.1. In eight infants operated on within three months of life, in whom not glaucoma caused the low vision, insufficient patching may have been of importance. However, five of them were operated rather late, during the third month of life, and some of them had undergone surgery because of after-cataract. It is therefore difficult to evaluate the importance of patching failure in the present series.

According to literature, virtually all children with unilateral congenital cataract develop strabismus. The critical period concerning development of motor fusion is probably the first 2 – 4 months of life (Birch, Shimojo et al. 1985; Mohindra, Zwaan et al. 1985; Archer, Sondhi et al. 1989). Too much patching of the intact eye prevents binocular visual development and may reduce vision in the intact eye (Thompson, Moller et al. 1996). Wright et al (1992) and Gregg & Parks (1992) who reported evidence of binocularity in very selected infants recommend reduced patching of the intact eye. For the first month or two virtually no patching was performed in order to allow for the development of binocular fusion (Wright, Matsumoto et al. 1992).

Three of the five eyes that required trabeculectomy had PFV and two of them developed buphthalmos. Apart from early surgery, PFV might have been a factor of importance for the development of severe glaucoma in the present series. Parks et al. (Parks, Johnson et al. 1993) found that the development of aphakic glaucoma was related to PFV and nuclear cataract, both of which are associated with microcornea. On the other hand, cataract extraction is recommended in eyes with PFV to prevent the increased likelihood of glaucoma from intraocular bleeding and/or shallow anterior chamber.

Although excellent results of treatment of dense unilateral cataract can be achieved in some infants who undergo cataract surgery and amblyopia treatment, few children attain binocularity and severe complications occur. The long-term patching therapy, which is necessary to avoid irreversible sensory deprivation amblyopia, is very demanding for the child and family and can cause extreme stress to parents and the parent – child relationship. Before the decision is taken to treat a monocular cataract, parents must be fully informed of the benefits and risks of surgical treatment and understand the importance of maintaining the prescribed regime concerning patching and contact lenses.

Thus, according to the results in the present unselected series of dense unilateral cataract, a good visual acuity may be achieved in children who undergo cataract surgery before 2 months of age and who adhere to the occlusion therapy schedule. However, complications often jeopardize the results.

4.1.3. Follow-up of complications requiring additional surgery in children operated for congenital cataract before 12 months of age (paper III)

Paper III presents a retrospective evaluation of complications leading to additional surgery in a consecutive group of children operated for bilateral (26) or unilateral (31) congenital cataract before 12 months of age. After the completion of the investigation accounted for in paper III, the children were followed-up for 4 years more. The median follow-up period is now 80 months (range 57 – 118 months). During this 4-year period, secondary surgery for after-cataract was performed in one eye each in two children while one child was subjected to trabeculectomy in one eye because of chronic glaucoma. A further child developed glaucoma and was medically treated bilaterally.

Ocular complications requiring additional surgery occurred in 48 of 83 eyes (in 37out of the 57 children). In all, 64 additional operations were performed.

The most frequent complication was after-cataract which occurred in 34 eyes and required 40 operations. The interval between primary cataract surgery and after-cataract surgery ranged from 2 weeks up to 4.5 years, with a median interval of 4 months. There was no difference in after-cataract incidence in unilateral cataracts as compared to bilateral cataracts ($\chi 2 = 1.46$; p 0.2).

After-cataract formation is more pronounced in children than in adults (Apple, Solomon et al. 1992). In this series of children operated on before the age of one year, secondary surgery of after-cataract was slightly more common in eyes that had

undergone the cataract extraction during the first 2 months of life but the difference was not statistically different.
The complications in the updated material and their relation to the age at which cataract surgery was performed are shown in Table 2.

	Unilateral cataract eyes	Bilateral cataract eyes	Surgery by 2 months (no. of eyes)	Surgery after 2 months (no. of eyes)	Surgery by 2 months (no. of eyes)	Surgery after 2 months (no. of eyes)
			Unilateral cataract	Unilateral cataract	Bilateral cataract	Bilateral cataract
After-cataract	10/31	24/52	6/14	4/17	15/28	9/16
Chronic glaucoma	5/31	8/52	4/14	1/17	8/28	0/16

Table 2. After-cataract and chronic glaucoma in unilateral and bilateral congenital cataract and their relation to the age at primary surgery.

After-cataract can cause amblyopia if not removed in time and secondary surgery implies risk for postoperative complications. The proliferating lens epithelial cells causing after-cataract with obstruction of the visual axis can also form a ring in the periphery of the capsular bag (Soemmering´s ring) which may be of importance for the pathogenesis of secondary glaucoma by affecting the anterior chamber angle (Kugelberg, Lundvall et al. 2000).
After-cataract surgery has been considered a risk factor for glaucoma (Chrousos, Parks et al. 1984; Lee, Lee et al. 1998). In this study vitrectomy for after-cataract preceded the development of chronic glaucoma in three out of nine children who developed glaucoma. In 20 other children (24 eyes) who underwent such surgery no glaucoma developed. In one child, however, who showed intense postoperative inflammatory response repeated vitrectomies on both eyes may have been important for the development of bilateral glaucoma. Glaucoma was not statistically more common in children who had undergone surgery for after-cataract. Similar experiences have been reported by others (Mills and Robb 1994; Magnusson, Abrahamsson et al. 2000). Secondary membrane surgery has also been implicated with retinal detachment (Chrousos, Parks et al. 1984). Retinal detachment occurred in one infant only (the infant with intense inflammatory response mentioned above). This complication can occur decades after cataract surgery (McLeod 1986; Francis, Ionides et al. 2001).
After-cataract surgery did not imply a lower visual acuity at follow-up (papers I, II). The VA of children operated for after-cataract was not different from that of children not treated for after-cataract, suggesting that the frequent checks and early vitrectomy in children developing after-cataract was effective in amblyopia prevention.
The development of pupillary block glaucoma soon after surgery occurred in 11 eyes (13 percent). Chronic glaucoma developed in 13 eyes (16 percent) during a median follow-up period of about 6.5 years. According to literature, eyes with small corneal size, nuclear cataracts and PFV are at greatest risk (Parks, Johnson et al. 1993). Such risk factors were present in all but one instance. Five eyes developing chronic

glaucoma had earlier been treated with vitrectomy for pupillary block, another risk factor. Even when treated, it may cause persistent anterior synechias leading to chronic glaucoma (Russell-Eggitt and Zamiri 1997).

Secondary glaucoma was not more common in eyes which had undergone after-cataract surgery (5/34) than in eyes not undergoing such surgery (8/49).

According to literature glaucoma is a common complication of cataract extraction. The incidence varies from 3 to 32 percent (Asrani and Wilensky 1995; Pandey, Wilson et al. 2001). Open angle glaucoma can develop slowly for years and decades after cataract surgery (Phelps and Arafat 1977; Russell-Eggitt and Zamiri 1997). It is therefore important that lifelong follow-up is planned for these children.

Secondary glaucoma requiring trabeculectomy occurred mainly in children who underwent cataract extraction in their first weeks of life. Five of nine children who underwent trabeculectomy had their primary operation during their first 2 weeks of life.

The higher prevalence of glaucoma in infants who undergo cataract extraction early is in accordance with other studies (Parks, Johnson et al. 1993; Mills and Robb 1994; Egbert, Wright et al. 1995; Magnusson, Abrahamsson et al. 2000). This may at least partly, be due to the type of cataract. Dense cataract present at birth is mostly of the nuclear type (Parks, Johnson et al. 1993).

The visual outcome was unsatisfactory in nearly all children developing glaucoma that required trabeculectomy. Only one such eye in the present study reached a VA over 0.1.

It is evident that there is a need for improved treatment methods in dense congenital cataracts. The etiologic and pathophysiologic mechanisms leading to glaucoma after cataract extraction have not been fully clarified. Many factors have been discussed in literature, such as Soemmering´s ring (Kugelberg, Lundvall et al. 2000) or surgery for after-cataract (Chrousos, Parks et al. 1984), postoperative inflammation, retained vitreous or lens material (Russell-Eggitt and Zamiri 1997), blockage or other dysfunction of the trabecular meshwork (Walton 1995).

After-cataract formation can be reduced in varying degrees with IOL depending on the design and composition of the lens. IOL implantation may also reduce the glaucoma incidence. In a review of literature Asrani et al. (Asrani, Freedman et al. 2000) did not find a single reported case of open-angle glaucoma after primary IOL implantation for congenital or developmental cataract. In their large collected series of congenital cataracts treated with IOL, only one case of glaucoma was found among 377 pseudophakic eyes compared with 14 eyes with glaucoma in 124 aphakic eyes. However, the mean age at the time of surgery of the children treated with IOL was 5 years and children with microcornea, PFV or other associated anomalies and systemic conditions were excluded. They suggested that in aphakia there is a loss of support to the trabecular meshwork and that the IOL might minimize this. They also hypothesized that the IOL might prevent access of vitreous chemical components to the anterior chamber.

In a survey of studies published after the report of Asrani et al. concerning IOL implantation in children similarly few instances of glaucoma are mentioned; only seven children out of 328 were mentioned in 12 such reports (Sharma, Pushker et al.

1999; Simons 1999; Dada, Dada et al. 2000; Lee and Kim 2000; O'Keefe, Mulvihill et al. 2000; Peterseim and Wilson 2000; Cassidy, Rahi et al. 2001; de Laage de Meux 2001; Lam, Seck et al. 2001; Lambert, Lynn et al. 2001; O'Keefe, Fenton et al. 2001; Wilson, Peterseim et al. 2001). However, many published series are selected, follow-up periods are short and few infants operated on during the first weeks of life are included. Other complications requiring secondary surgery have been frequent in some series. Nevertheless, IOL implantation may be a better alternative to aphakia in cataract treatment even in small infants. It is therefore relevant to study intraocular lenses designed for small eyes (papers IV and V).

4.2. Studies on rabbits

4.2.1. Bilateral lensectomy with implantation of a downsized HSM PMMA intraocular lens with long haptics in one eye (paper IV)

In this study the effects of a downsized single-piece biconvex heparin surface modified PMMA IOL, +21 D designed for small eyes were investigated in an animal model (Figure 4). The haptics are long enough to form a ring when implanted in the capsular bag in order to decrease the formation of after-cataract. The size of the IOL was chosen on the basis of rabbit and human lens sizes. The mean diameter at birth and at 6 to 9 months was reported to be 6.0 and 7.7 mm, respectively. We have estimated that the lens of the 3-week-old rabbit has a diameter of approximately 7.5 mm. The overall diameter of the IOL chosen is 7.8 mm. The optic has a diameter of 4.5 mm. Following clear lens extraction performed in both eyes in 3-week old rabbits, one randomly selected eye was implanted with the IOL.

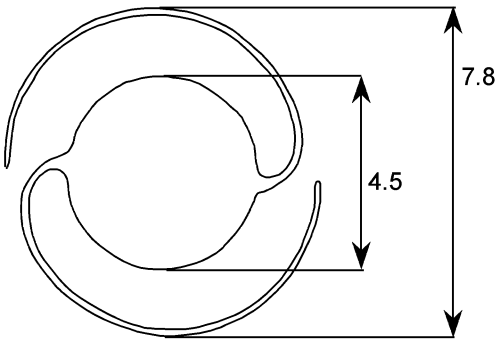

Figure 4. Downsized HSM PMMA IOL.

The IOL remained well centred in all eyes and no IOL dislocation occurred. It markedly decreased the formation of after-cataract. In most eyes implanted with the present IOL only very small amounts of after-cataract developed (median weight 30 mg) as compared to considerable amounts of after-cataract masses in aphakic eyes (median weight 250 mg).

Implantation of an IOL of regular size or a capsule tension ring (Kugelberg, Zetterstrom et al. 1997a,b) has been shown to decrease the formation of secondary

cataract in the infant rabbit eye. The incidence of posterior capsule opacification in humans after extracapsular cataract extraction is lower in eyes implanted with posterior chamber IOLs compared with those in non-implanted eyes (Apple, Solomon et al. 1992). The migration of lens epithelium cells from the periphery to the posterior capsule seems to be mechanically reduced with an IOL or a capsule tension ring implanted in the capsular bag. The haptics of the present lens were long enough to form a circle when implanted in the bag. The hypothesis was that the haptics might function as a capsular ring filling out the whole circumference of the capsular bag and thereby decreasing the migration of lens epithelium cells and the formation of after-cataract more effectively.

Animal studies have shown that implantation of regular sized PMMA-IOL retards eye growth, possibly because of injury to the growth area of the growing infant eye (Kugelberg, Zetterstrom et al. 1997). The smaller IOL used in this study was designed in an attempt to decrease the after-cataract formation without disturbing the eye growth process. However, the study indicates a retardation of the eye growth even with the present smaller lens. The estimations of corneal diameter growth gave similar results. The retardation of axial length growth was most pronounced during the first two months after surgery.

The proliferation of lens epithelium cells after lensectomy is pronounced, particularly in the periphery of the capsular bag. Theoretically this might cause partial or total closure of the angle and trabecular meshwork, with the development of secondary glaucoma as a consequence (Kugelberg, Lundvall et al. 2000).

At the completion of the 6 months study with 15 animals signs of glaucoma had developed in seven animals, in five eyes without IOL and in four eyes with IOL. Four animals were sacrificed within the age of 2 months because of severe buphthalmos. One of them developed buphthalmos in the pseudophakic eye during the first month after surgery. One developed bilateral buphthalmos and two developed buphthalmos in the aphakic eye during the second month after surgery.

Thus, in spite of the much lower tendency to after-cataract formation in the pseudophakic eyes, glaucoma occurred although not more frequently than in the aphakic eyes.

The glaucoma incidence was extremely high in this rabbit series in pseudophakic eyes as well as in aphakic eyes. More than half of the animals developed glaucoma.

It is obvious that the results in animal experiments have to be evaluated with caution and cannot be transferred to humans without strong reservations. Although the rabbit is commonly used in ocular research, this species has a labile blood-aqueous barrier and a high propensity for inflammatory response to experimental procedures, especially so in infant rabbits (Bito 1984). This may explain the high glaucoma incidence. It has also been suggested that the rabbit is unsuitable for experiments concerning biocompatibility testing of IOLs extending over periods longer than 3 months (Bito 1984; Norton, Kohnen et al. 1999). Furthermore, it is possible that the litters used in the study had an abnormal disposition to glaucoma development.

Thus the downsized HSM-PMMA IOL with long haptics forming a ring in the capsular bag markedly decreased the production of after-cataract and the IOL remained well centred in all eyes. The glaucoma incidence was high in aphakic as

well as in IOL implanted eyes possibly because of an abnormal disposition to glaucoma development in the rabbit litters used.

The bulb growth was compromised in pseudophakic eyes during the first 2 postoperative months.

The results merit testing a downsized PMMA IOL against standard lenses used in infants.

4.2.2. The effect of 3-piece Acrysof® and downsized HSM PMMA intraocular lenses on infant rabbit eyes (paper V)

This animal study was undertaken in the search for an IOL suitable for very small eyes. Ideally such a lens should remain in place without tendency to subluxation, allow normal eye growth and prevent after-cataract and glaucoma. The effects of a downsized single-piece biconvex heparin surface modified PMMA IOL (Figure 5), + 21 D (with optic size 5.0 mm and an overall diameter of 7.8 mm) designed for small eyes was compared with a biconvex 3-piece Acrysof® IOL (Figure 6), + 21 D (with optic size 5.5 mm and overall length 12.5 mm). The PMMA IOL was provided with haptics long enough to form a ring when implanted in the capsular bag. Clear lens extraction was performed in both eyes in 3-week old rabbits, which have capsular bag size of approximately the same size as that of newborn infants. In one group of rabbits one randomly selected eye was implanted with the PMMA IOL and in another group the 3-piece Acrysof® IOL was implanted. The fellow eyes were left aphakic.

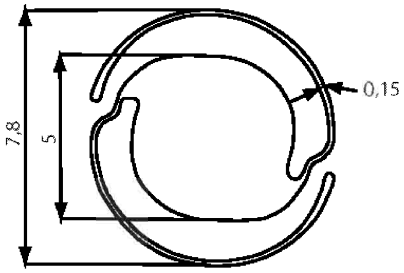

Figure 5. Downsized HSM PMMA IOL.

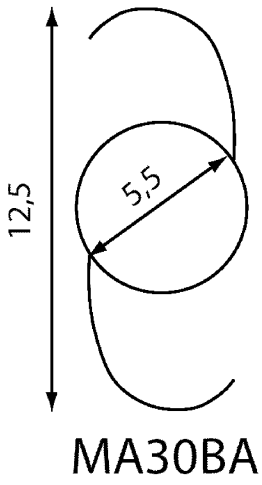

Figure 6. 3-piece Acrysof® IOL.

The downsized PMMA IOL remained well centred in all animals and no dislocation occurred. However, all eyes implanted with the 3-piece Acrysof® IOL showed anterior movement of the optic resulting in an occluded pupil and a shallow anterior chamber. The 3-piece Acrysof® lens was bistable and when the haptics were compressed to 7.5 mm, the haptics bent backwards or forwards giving a sagittal depth

of the lens of about 3.5 mm. The haptics of the PMMA lens were more flexible and when compressed to 7.5 mm, the sagittal depth of the lens was 0.5 mm.

The 3-piece Acrysof® IOL has been used in children 4 – 19 weeks old at surgery (Lambert, Lynn et al. 2001). There was no mention of lens dislocation, which implies that the conditions in the capsular bag of the child differ from those of the animals used in the present study. It is possible that the capsular bag in children 4 – 19 weeks old is large enough or has compliance enough to prevent the dislocations found in this animal experiment. However, in view of the dislocation of the lens with occlusion of the pupil in infant rabbit eyes implanted with the 3-piece Acrysof® IOL, the surgeon should be cautious about using this lens in eyes of newborns or in eyes with severe microphthalmia.

After-cataract is a common complication after lens extraction in children implying reduced sight and risk of amblyopia. It often requires secondary intervention, which can have ophthalmic complications such as postoperative inflammation.

The after-cataract formation in eyes implanted with the downsized PMMA IOL (median 3 mg; range 0–11 mg) and in eyes implanted with the 3-piece Acrysof lens (median 26 mg; range 11–119 mg) was markedly reduced compared to that in aphakic eyes (median 171 mg; range 48–322 mg).

A number of factors influence the reduction of after-cataract formation following IOL implantation. A full-size IOL with complete refilling of the capsular bag reduced after-cataract formation more effectively than smaller lenses (Assia, Blumenthal et al. 1999). On the other hand, a 10 mm tension ring (without lens) effectively reduced the after-cataract formation in newborn rabbit eyes (Kugelberg, Zetterstrom et al. 1997a).

In spite of the small optic, the PMMA IOL reduced after-cataract formation more effectively than the 3-piece Acrysof® IOL, probably because of the long haptics which formed a ring in the capsule periphery and thereby inhibited migration of the residual lens epithelial cells.

Glaucoma developed in the eye implanted with the regular-sized 3-piece Acrysof® IOL in one animal and in the aphakic eye of another animal. No animal with the downsized lens developed glaucoma.

The incidence of glaucoma in this animal experiment performed on growing rabbits was much lower than in another similar study of clear lens extraction with or without IOL implantation (paper IV). The difference is probably largely due to differences in the lengths of observation periods. In the former study (paper IV), the observation period was 6 months, in the present study it was reduced to 3 months.

There was no significant difference in axial length growth between eyes implanted with the downsized HSM PMMA IOL and the aphakic eyes or between eyes with the 3-piece Acrysof IOL and aphakic eyes. There was no significant difference in axial length growth between the 3-piece Acrysof® IOL implanted and the PMMA implanted eyes. Earlier studies have shown that clear lens extraction caused a retardation of axial growth as compared with phakic control animals (Kugelberg, Zetterstrom et al. 1996). This retardation was enhanced if the extracted lens was substituted with a regular-sized PMMA IOL (Kugelberg, Zetterstrom et al. 1997b). In the present study the retardation of the axial length growth in the pseudophakic eyes did not significantly differ from that of the aphakic eyes.

Thus, the present two lens models markedly reduced the after-cataract formation. The downsized PMMA IOL with long loops inhibited the after-cataract production more effectively. No animal implanted with the downsized IOL developed glaucoma. The downsized PMMA IOL remained well centred while the 3-piece Acrysof® lens dislocated. The downsized PMMA IOL merits further testing.

Surgeons should use caution before implanting the 3-piece Acrysof® lens in eyes of newborns or in eyes with severe microphthalmia.

5. Summary and Perspectives

Summary:

Congenital bilateral cataract is the most common cause of treatable childhood blindness. The visual outcome in infants undergoing surgery for *bilateral* congenital cataract has improved considerably because of improved surgical methods and the realisation that early detection, allowing early cataract extraction and immediate optical correction, can prevent otherwise irreversible deprivation amblyopia. The results in *unilateral* cataract have in general been less favourable due to the interocular competition. Good visual results have been recorded in selected cases, which require early surgery, accurate optical correction and excellent compliance with the occlusion therapy. Another condition is absence of severe complications. Despite improved surgical technique, complications following early surgery for congenital cataract are common, the most important being glaucoma. Glaucoma occurring soon after surgery is in most cases due to pupillary block. Both chronic open-angle and chronic closed-angle glaucoma occur. Open angle glaucoma can develop many years, even decades after early surgery so that the patients have to be followed throughout their lives.

In developing or partial cataract, the visual input may be sufficient to allow a normal development of the visual nervous system. In such children amblyopia may not be a problem. The present study concerns congenital cataract, dense from birth.

The main aims of the project were to account for complications and long-term functional results of cataract surgery in an unselected consecutive series of children with dense congenital cataracts operated on before the age of 12 months.

Complications requiring additional surgery were very common in these infants. After-cataract requiring reoperation developed in more than one third of the cataract-extracted eyes. Chronic glaucoma developed predominantly in children who had their cataract extraction very early. Microphthalmos seemed to be a risk factor as well as persistent foetal vasculature. Secondary glaucoma was not more common in eyes operated on for after-cataract. In *bilateral* cataract good visual outcome was achieved in most otherwise healthy children if the surgery was performed before 6-8 weeks of age. In *unilateral* cataract a good visual outcome was achieved only in children who underwent surgery early but chronic secondary glaucoma leading to blindness of the aphakic eye developed in three out of 12 children with unilateral cataract operated on before 6 weeks of age.

In adults the introduction of intraocular lenses (IOL) implants is epoch-making. IOLs are also implanted in children but they are usually not recommended in children before 12 months of age. Implantation of intraocular lenses designed for small eyes may, however, be an alternative to aphakia also in newborns. One aim of the study was to test such lenses in infant rabbits.

The effects of one-piece PMMA IOLs designed for small eyes with long haptics forming a ring in the capsular bag were investigated in infant rabbits and compared to a conventional 3-piece Acrysof® IOL and aphakia. The 3-piece Acrysof® IOL was strongly deformed in these small eyes and the vaulting of the lens caused occlusion of the pupil. This type of lens should probably be avoided in very small eyes. The

PMMA IOLs designed for small eyes remained well centred and did not dislocate in any animal. Considerable after-cataract developed in all aphakic eyes. The IOLs reduced or prevented the formation of after-cataract, the PMMA IOL more effectively than the 3-piece Acrysof® IOL. Glaucoma occurred in pseudophakic eyes as well as in aphakic eyes.

Perspectives:

The pathophysiology of chronic glaucoma developing after cataract surgery is mainly unknown and should be an important research subject in the future.

Randomised studies concerning the complications and functional results after early surgery in dense cataract, with and without IOL implantation, are urgently needed and have started in the USA.

Systematic studies to determine the optimal interval for surgery, during which the balance between functional results and occurrence of complications is most favourable, are needed.

It can be expected that IOLs more suitable for the infant eye may decrease the incidence of complications. Continued research concerning methods to decrease the lens epithelial proliferation and the postoperative ocular inflammatory and proliferative reactivity is needed. Cell-inhibitor coating of the IOL may be an option.

Systematic studies concerning optimal patching strategy in unilateral cataract may improve the functional results.

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