EXTRACAPSULAR CATARACT EXTRACTION

The fate of retained lens material and intraocular lenses

EXTRACAPSULAIRE LENS EXTRACTIE

Het lot van het achtergebleven lensmateriaal en de intraoculaire lens

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit van Rotterdam
op gezag van de Rector Magnificus
Prof. dr. A.H.G. Rinnooy Kan
en volgens besluit van het college van dekanen.

De openbare verdediging zal plaatsvinden op
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door

Johannes Pieter Kappelhof
geboren te Breda

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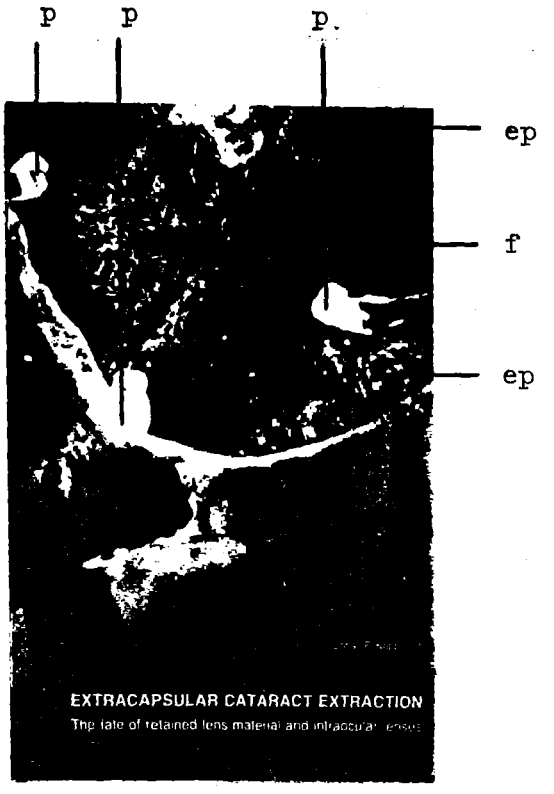
ERRATA

Blz. 8: De onderste regel kan geheel vervallen

Blz. 129 (curriculum vitae): "was" in de laatste zin dient vervangen te worden door "is".

Bijschrift bij de omslagfoto

De pupil van een 80-jarige patiente 53 maanden na extracapsulaire cataractextractie met implantatie van een medallion iridocapsulaire kunstlens, gezien vanaf posterior (dus a.h.w. door de pupil naar buiten kijkend). In de pupilopening zijn Elschnigse parels (ep) en fibroblasten (f) op het achterkapsel zichtbaar en tevens drie van de vier plaatsen (p) waar de twee pootjes van de kunstlens zijn bevestigd aan de lens (vergelijk fig. 3 blz. 6). Onderop de foto is vaag een deel van de ring van Soemmerring zichtbaar.



Aan mijn ouders

Contents

1. Introduction.

1. INTRODUCTION

1.1. Cataract as cause of loss of vision

Clinically cataract is defined as a significant decrease of vision due to an irreversible increase in absorption or scattering of light by the lens. A cataractous impairment of vision is always progressive although the speed of progression may vary greatly. A cataract caused by a perforating injury may lead to opacification within a few hours whereas senile cataractous changes may take many years to reach a significant loss of vision and therefore can give the impression of being stationary (1). Whatever the etiology might be, primary cataract as a rule leads to social blindness because most types of cataract tend to be bilateral.

1.2. Epidemiological data on cataract and its treatment

Cataract is the most common cause of blindness all over the world (2) with a high incidence amongst the older in the developing countries. As we know from the data of the World Health Organisation, more than 40 million of blind people are living in the world and half of them lost their vision due to cataract (3,4). Each year vision obstructing lens opacities are being formed in more than one million humans (2). The frequency of cataract in the U.S.A. has been stated in the Framingham Eye Study to be 4.6 % in the age range of 52-64 years, 18.1 % in the age range of 65-74 years and 46.1 % in the age range of 75-80 years (5). These figures are higher in countries with a tropical climate and the overall frequency of senile cataract has been found to be as high as 52.3 % in Punjab, reaching values of 83.3 % in individuals of over 80 in that area (6).

The above figures illustrate the socio-economic magnitude of the problem of cataract and stress the importance of evaluating optimal treatment as well as searching for preventive treatment. There are some 80 different drugs and eye drops against cataract but none of them has been proven to be efficacious.

Treatment of cataract

Treatment of cataract is known since ancient times and originally consisted of pushing away the lens from the optical axis of the eye in the vitreous

cavity. Nowadays the cataractous lens is removed from the eye. Cataract extraction takes the sixth place in frequency among the large operations (7) and is the main cause of ophthalmological hospital admission in the U.S. (8). In 1983 over 600,000 cataract extractions were performed in the United States (9) and 90,000 in the Federal Republic of Germany (4). In 1984 this figure amounted to 813,000 in the United States and it is extrapolated on demographic grounds that this number will increase to 1,937,000 in 1990 (10). This means a steady increase in work load for ophthalmic surgeons but also an increase in postoperative complications to be expected.

Surgical extraction of the cataractous lens can be carried out intracapsularly and extracapsularly. Intracapsular cataract extraction means mechanical or chemical disruption of the zonular fibers (or suspensory ligaments) of the lens followed by removal of the whole lens including the lens capsule. Intracapsular cataract extraction is nowadays only rarely performed in the Academic Hospitals in The Netherlands due to a higher incidence rate of long term complications. In the extracapsular procedure the anterior lens capsule is opened after which the lens content, including lens fibers and the majority of the epithelial cells, can be taken out by several methods. In this way the posterior and equatorial parts of the capsular bag, attached to the ciliary processes by the zonular fibers, remain in place. A schematical representation of this procedure is given in Fig. 1.

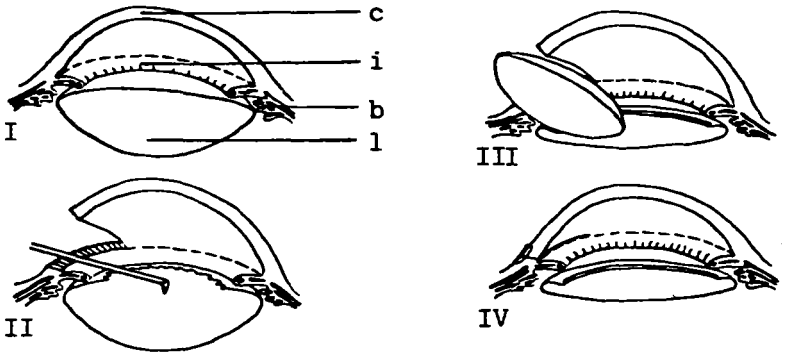


Fig. 1: Schematic representation of the extracapsular cataract extraction procedure. I: normal anterior segment of the human eye with cornea (c), iris (i), ciliary body (b) and lens (l). II: incision of the anterior capsule with a hooked needle after making the corneal or corneoscleral incision. III: expression of the lens nucleus. IV: the empty capsular bag after the operation, here without intraocular lens.

Correction of the postoperative refractive error

Before 1949, when Harold Ridley introduced the acrylic intraocular lens, glasses with powerful convex lenses were used to correct the refractive error of the aphakic eye. Gradually it became clear that intraocular lenses and contact lenses optically are better alternatives for aphakic correction. For the patient's comfort intraocular lenses are the best choice and they are used with increasing frequency. In fact insertion of artificial intraocular lenses during cataract surgery is nowadays more or less the rule and the number of so-called secondary implantations is also increasing. Secondary implantation means insertion of an intraocular lens after an intra- or extracapsular lens extraction at an earlier date. An eye without the crystalline lens is called an aphakic eye; an eye with an intraocular artificial lens after lens extraction is called a pseudophakic eye. In 1983 more than 70 % of the cataract operations were with an intraocular lens implant in the United States (9). In 1984 800,000 lens implantations (including secondary implantations) were performed in this country and this number is extrapolated to increase to 2,003,000 in 1990. This last figure is actually higher than the number of estimated cataract extractions due to secondary implantations. The estimated number of intraocular lens implantations outside the United States will increase from 200,000 in 1984 to 1,228,000 in 1990 (10).

1.3. Intraocular lenses and ocular interactions.

Types of intraocular lenses

Since the introduction of intraocular lenses in 1949 over two hundred lens types have been manufactured after the design of different surgeons all over the world. By the place and method of fixation they can be divided in three main types i.e. anterior chamber lenses, iris supported lenses and posterior chamber lenses. The anterior chamber lens is placed anteriorly to the iris and uses the angle recess for fixation purposes. Iris supported lenses are placed anteriorly to the iris and they are fixed to the iris by sutures, loops or claws. The third type, the posterior chamber lens is placed posteriorly to the iris.
The intraocular lenses mentioned in chapters 2, 4, 5 and 6 of this thesis are either iris supported lenses or posterior chamber lenses. The most customary types will be described here.

The Binkhorst 4-loop or iris-clip is an iris-fixated lens and has four poly-

propylene or polyamide loops of which two are to be placed anterior to the iris and two posterior to the iris (Fig 2a). The polymethylmethacrylate (PMMA) optic is placed in front of the iris in the pupillary aperture (fig 2b).

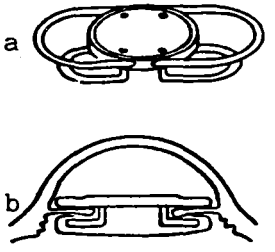


Fig. 2a:The iris fixated lens. b: The iris fixated lens as it is placed in the eye.

The medallion iridocapsular lens and the the Binkhorst 2-loop iridocapsular lens are two iris supported lenses and both lenses have two polypropylene loops which are to be placed behind the iris preferably in the capsular bag. The PMMA optic is also placed in front of the iris (Fig 3a and b).

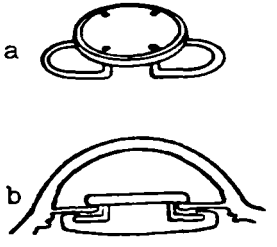


Fig. 3a: The iridocapsular lens. B: The iridocapsular lens as it is placed in the eye.

The posterior chamber lenses mentioned in this thesis are the Pearce Tripod lens, a modified tripod lens and the J-loop lens. The Pearce tripod posterior chamber lens is a rigid PMMA lens with two short loops and one longer loop (Fig 4a). After extracapsular cataract extraction the two short loops are placed inferiorly in the capsular bag and the longer loop is placed superiorly in the ciliary sulcus (fig 4b).

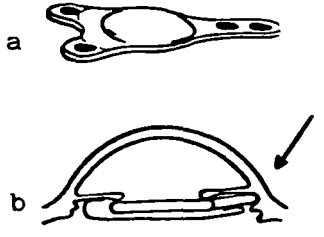


Fig. 4a: The Pearce posterior chamber lens. b: The Pearce lens as it is placed in the eye. Arrow points to the ciliary sulcus.

The modified tripod lens consists of a rigid tripod lens with two additional polypropylene loops.

The J-loop lens (Fig 5a) has a circular PMMA optic with two J-shaped, polypropylene loops which are both to be placed in the capsular bag (Fig 5b).

a

b

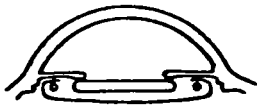


Fig. 5a: The J-loop posterior chamber lens.
b: The J-loop posterior chamber lens as it is placed in the eye.

Ocular interactions

However common the insertion of intraocular lenses after extracapsular cataract extraction in modern cataract surgery might be, the procedure is not without complications. Apart from direct surgical complications as e.g. wound dehiscence or peroperative or postoperative haemorrhage, the following major complications can be distinguished (11): i) inflammations, ii) corneal complications, iii) iris complications, iv) complications of lens implant position, v) opacification of the media, vi) mechanical complications caused by the intraocular lens, vii) complications related to possible bioincompatibility of the materials used in the manufacturing of the intraocular lenses, viii) manufacture defects, ix) retinal complications and exacerbations of preexisting disease . Extensive descriptions of these complications are available in literature and only a few will be discussed here with an emphasis on the opacification of the media.

Postoperative opacification of the media is the most common complication of extracapsular cataract extraction and it is not necessarily dependent on the presence of an intraocular lens. It is disappointing for the patient to experience after an apparently uncomplicated surgical removal of the cataractous lens that vision becomes blurred again. Apple (1984) divided the postoperative opacifications of the media in pupillary and cyclitic membranes, perilenticular or "coccoon" membranes, precipitates on the lens optic and opacification of the posterior capsule (after-cataract) (11).

Pupillary and cyclitic membranes are complications associated with older lens types and they are seldom seen nowadays.

Perilenticular or "coccoon" membrane formation following organization of fibrin, inflammatory and/or hemorrhagic debris deposited on the lens has always been a rare complication.

Precipitates on the lens optic were considered to occur only incidentally. However, the available literature suggests the common presence of a limited foreign body reaction in the human anterior segment of the eye after insertion of the intraocular lens. This foreign body reaction gives rise to proliferation of fibroblast-like cells on the acrylic surface of an intraocular lens (12, 13, 14, 15). These cellular elements were first described on intraocular lenses explanted from eyes after serious complications. Most of these lenses had been in the eye for at least several months. Light microscopy revealed the presence of macrophages, epitheloid cells and giant cells together with an acellular proteinaceous coating on the surface of the intraocular lens. The presence of probably identical cellular elements on the anterior surface of the lens was noted by specular microscopy in a great number of uncomplicated cases of intraocular lens insertion shortly after operation, indicating that this limited foreign body reaction is not an incidental but a more general phenomenon.

Opacification of the posterior capsule or after-cataract is the most common of the four types of opacification of the media. It is believed to be caused by residual subcapsular or equatorial lens epithelium undergoing fibrous metaplasia or forming Elschnig's pearls (Fig. 6).

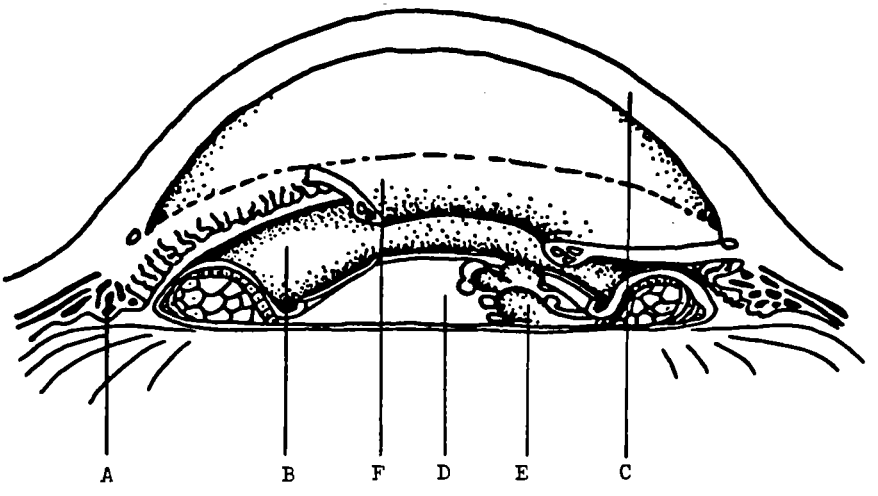


Fig. 6. Schematical representation of the anterior segment of the eye after extracapsular cataract extraction without implantation of an intraocular lens. Posterior to the partially dissected iris (F) the Soemmerring's ring is visible (B) with Elschnig's pearls (E) on the posterior capsule (D). A: ciliary body, C: cornea, F: iris.

3. The anterior capsule of the cataractous lens in human.

After-cataract is reported in 40 % to 50 % after two to five years of follow-up (17, 18, 19, 20). These figures refer to studies of cataract extractions either without lens implantation or with implantation of anterior chamber or iridocapsular lenses. After posterior chamber lens implantation the incidence of posterior capsule opacification was reported by Lindstrom and Harris (1980) to be 18.4 % after 24 to 36 months (21). Nishi (1986) noted this complication to occur in 7 % of the cases three to four years after implantation of a posterior chamber intraocular lens and in 9.3 % after four to five years of follow-up (22). Comparison of the latter figures with the previously mentioned 40 to 50% value points to a lower incidence of posterior capsule opacification after implantation of posterior chamber intraocular lenses, as was previously suggested by various authors (21, 22). This phenomenon is explained by assuming that the posterior chamber intraocular lens acts as a mechanical barrier and prevents migration of proliferating lens epithelial cells on the posterior capsule (22).

1.4. The aim of this study

The aim of this study was to examine the fate of the lens material that remains in the eye after an extracapsular cataract extraction both with and without insertion of an intraocular lens. Apart from this, the development of precipitates on the intraocular lenses was morphologically investigated in order to get a better understanding of the interactions between eye and intraocular lens.

This thesis is divided into a first part covering animal experiments and a second part about morphological studies on human material, i.e. autopsy eyes or explanted intraocular lenses. For obvious reasons it is nearly impossible to obtain human eyes after a short implantation time. Therefore in order to study the early events I had to turn to an animal model. Between these two parts we have summarized our data on human anterior lens capsules obtained from extracapsular cataract extractions.

Animal experiments

We performed extracapsular extraction of clear lenses without implantation of intraocular lenses to study the reaction of the retained lens material undisturbed by the presence of a foreign body. The ultrastructural features

of the retained lens material were examined after varying survival times (chapter 2.1).

In another experiment extracapsular cataract extraction with implantation of a posterior chamber lens was performed and the deposits on the anterior surface of the intraocular lens were investigated by scanning electron microscopy after short survival times. This is described in chapter 2.2.

Morphological studies on human pseudophakic eyes and explanted intraocular lenses

The ultrastructural study of parts of the human anterior capsule and a short review of the relevant literature is given in chapter 3. To compare experimental and human data we studied a number of post mortem human eyes. These eyes had been treated by extracapsular cataract extraction with implantation of an intraocular lens. All lenses were of the iris-fixated or iridocapsular type. The morphology of the doughnut-shaped lens material was investigated and compared with the results from the rabbit experiment (chapter 4.1.). Four specimens contained globular material on the posterior capsule; the so-called Elschnig's pearls. They occurred in varying stages of development and they are described in chapter 4.2. A schematical representation of the anterior segment with the so-called Soemmerring's ring and Elschnig's pearls is given in Fig 6.

Chapters 4.3 and 4.4 are devoted to the ultrastructural morphology of deposits on intraocular lenses that have been removed from pseudophakic eyes with serious postoperative complications as well as some structural defects of the intraocular lenses or suturing materials.

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2. Extracapsular cataract extraction and intraocular lens implantation in the rabbit

2.1. The ring of Soemmerring in the rabbit: a scanning electron microscopic study (Graefe's Archive for Clinical and Experimental Ophthalmology 223: 111-120, 1985).

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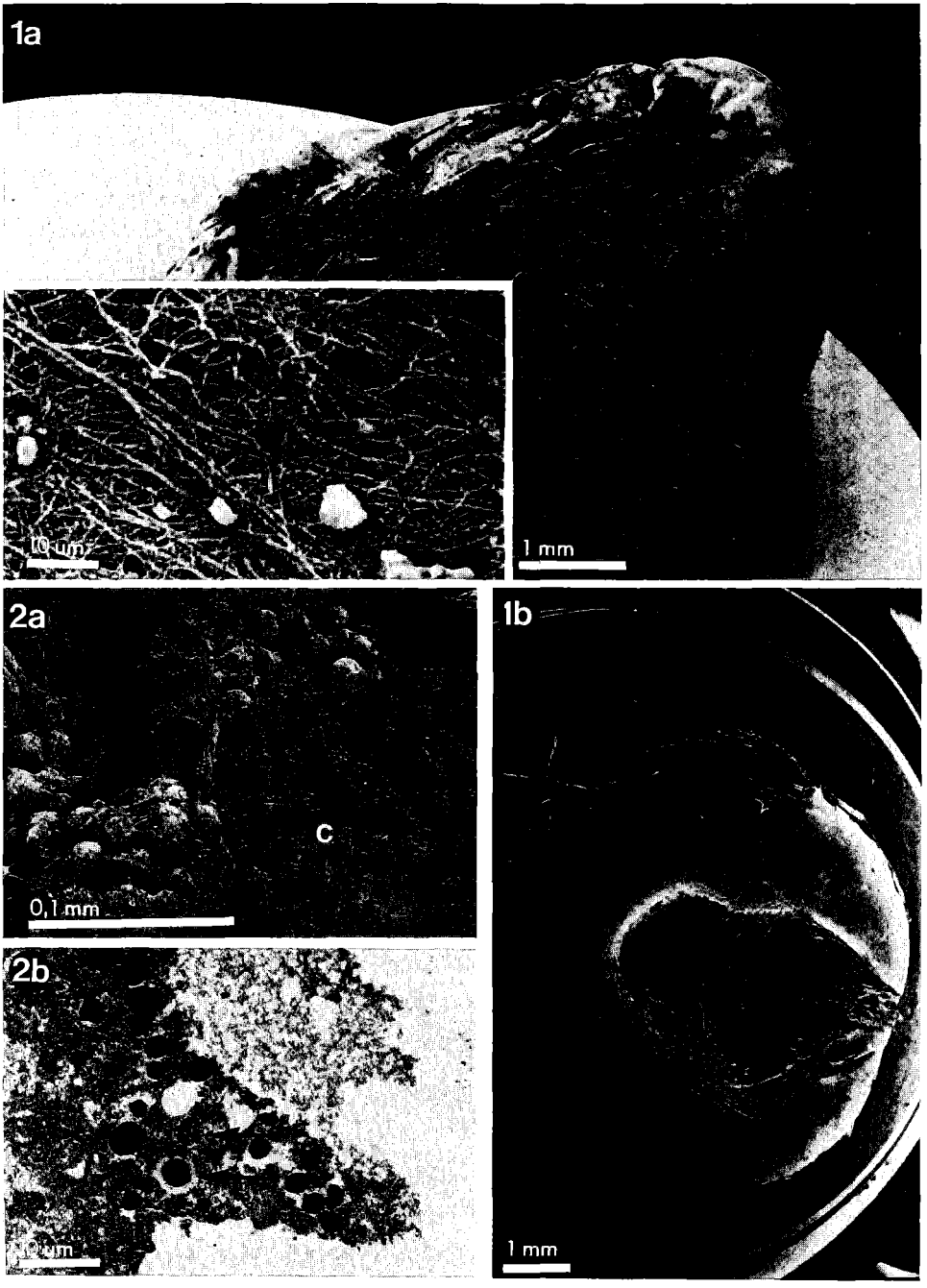
Abstract. The scanning ultrastructure of the remnants of the lens left in the eye after extracapsular lens extraction was investigated in the rabbit. Extracapsular lens extraction was performed in 25 eyes and the development of after-cataract followed by biomicroscopic examination. After survival times varying between 1 week and 12 months, the eyes were enucleated and the rings of Soemmerring treated for for light microscopy and scanning and transmission electron microscopy. Soemmerring's ring consisted of the fused remnants of the dissected anterior and posterior lens capsule, enclosing the equatorial part of the former lens, left behind after the operation. The anterior capsule and, to a lesser extent also the posterior capsule were multilayered and appeared to be thickened. While the remnant of the anterior capsule was lined by a monolayer of epithelial cells, the posterior part of the capsule was only partly lined by irregularly arranged epithelial cells. All epithelial cells were highly vacuolized. In transection the interior part of the ring consisted of normal fibers, irregularly oriented and irregularly shaped fibers, degenerated fibers, and globular amorphous masses. Many of the normal fibers contained cell nuclei. At the equator and at the posterior side of the fusing anterior and posterior capsule as well, the fiber organization resembled the lens bow region of normal lenses. Frequently, islands of epithelial cells were observed in the center of the ring. The vitreal face of the posterior capsule in the center of the ring (in the optic axis of the eye) seemed to be unchanged and on its pupillary surface, fibers of different size as well as fibroblast-like cells were found. However, clear-cut Elschnig's pearls were absent. Our results are compared with the observations summarized in the literature. It can be concluded that the epithelial

cells in Soemmerring's ring retain their capacity for division and differentiation. The newly formed fibers seem to be pushed to the center of the ring and to degenerate.

Introduction

One of the major problems encountered in extracapsular cataract extraction in human eyes is the formation of after-cataract membranes, i.e., the in vivo development of opacifying changes on the posterior lens capsule. The first descriptions of after-cataract following an extracapular cataract extraction were Dietrich in 1824 and Cocteau and Leroy-d'Etiolle in 1827 (reviewed by Duke-Elder 1969). After-cataract in man was noticed by Soemmerring (1828), and the remnants of the peripheral parts of the lens have been named after this ophthalmologist from Gottingen: Soemmerring's ring. Elschnig (1911) performed light-microscopic examinations and offered some case histories on human material. The globular lens remnants on the posterior lens capsule, first described by Hirschberg in 1901, are called Elschnig's pearls or bladder cells. Duke-Elder (1969) reviewed the light-microscopic investigations in after-cataract formation and classified lens remnants in three groups: capsular remains; capsulolenticular remains; pigmentary, hemorrhagic, and inflammatory fibrous elements. In a detailed paper, McDonald et al. (1974), have described the formation of after-cataract in the rabbit using transmission electron microscopy and autoradiography. According to the literature the ring of Soemmerring is formed by the fusion of the anterior and posterior capsule enclosing (within its walls) a viable amount of lens cortex and proliferating and degenerating epithelial cells. This results in a doughnut-shaped capsular structure. The middle of the ring consists of the posterior capsule and it is this capsule, in the axis of the eye, that obstructs vision when it becomes opaque. Unless sector iridectomy has been performed or aniridia is present, or unless the pupil is sufficiently dilated, the ring itself is hidden by the iris.

As part of a study on laser treatment of after-cataract and as an introduction to a study on human material, we investigated the morphology of after-cataract in the rabbit by light microscopy (LM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). The main purpose of this study was to investigate the scanning ultrastructure of normal and distorted lens fibers in the ring of Soemmerring and the adherent structures on the posterior capsule. In a period of increasing use of the extracapsular cataract-extraction technique in man, reinvestigation of the structure of the retained lens material seems necessary, as we still do not know why the capsule remains clear in some patients, while in others it becomes fibrotic. Some patients never acquire Elschnig's pearls and others need removal three times a year.


1a
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1 mm
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Material and methods

Adult Dutch pigmented rabbits with clear lenses were used in this study. The lenses of 25 eyes were extracted extracapsularly. The main problem in this operation was to keep the pupil dilated and to get as little fibrin formation as possible. From the preoperative day 3 on, indomethacin eye drops (0.5%) were given together with atropin (1%) three times a day. Every 15 min during the 2 h before the operation atropin (1%), fenylephrin (10%), cyclopentolate (1%), and tropicamide (0.5%) eye drops were administered. The operation was performed under a microscope with coaxial illumination. The anterior lens capsule was opened along the pupillary border with the can-opener technique using a bent disposable 27-gauge needle on a syringe filled with air. This needle was stabbed through the cornea without prior incision. From the stab wound a corneal incision was made. The anterior capsule was grasped with Vogt capsule forceps. Because of the positive vitreous pressure, it was easy to wash out the lens nucleus with an olive cannula and Ringer's solution. By then, however, the iris had become so hyperemic and the pupil so narrow that it was impossible to wash out the peripheral lens remnants under direct visualization. To prevent bleeding and more fibrinous formation no peripheral iridectomy was done. The corneal incision was closed in two layers: the deep one with 10.0 nylon, suturing Descemet's membrane; the superficial one with with 50 um stainless steel wire. Postoperatively, 5 mg bethamethasone was injected subconjunctivally. The first postoperative day we saw a fibrinous reaction in the anterior chamber with the development of posterior synechiae. For one week after the operation, atropin 1%, dexamethasone (0.1%), and indomethacin 0.5% eye drops were given.

The development of after-cataract was followed by biomicroscopy and after survival times varying from 1 week to 12 months, the animals were killed by an overdose of pentobarbiturate (Nembutal). The eyes were immediately enucleated and placed in a cacodylate-buffered glutaraldehyde/formaldehyde fixative (Peters, 1970). The posterior part of the globe was cut off and the anterior segment was stored in the same fixative for several weeks to months.

For scanning electron microscopy of the zonular fibers one anterior segment (8 months survival time) was prepared as a whole. From the other eyes Soemmerring's rings were extracted. The specimens were thoroughly rinsed in cacodylate buffer, dehydrated in a graded series of ethanols and critical point dried with CO_2 (see Willekens and Vrensen, 1981). The specimens were glued on SEM specimen mounts with conductive carbon cement and subsequently gold-coated. The specimens were examined in a Philips SEM 505 scanning electron microscope using a secondary electron detector. After inspection, the specimens were removed and fragmented and the newly exposed faces were gold-coated. Some smaller speci-

mens were mounted on special metal plates and studied in a Philips EM 400 electron microscope using the back-scatter detector.

For transmission electron microscopy, the specimens were postfixed in OsO_4 and, after dehydration in ethanol, embedded in Epon 812. Semithin and ultrathin sections were cut and stained with toluidine blue and uranyl acetate/lead citrate, respectively. The ultrathin sections were studied in a Philips EM 201 electron microscope.

For light microscopy several specimens were rinsed and dehydrated in a graded series of ethanol for 2 weeks and embedded in nitrocellulose.

Table 1. Postoperative survival time of rabbits, together with number of eyes examined

Postoperative survival time	Number of eyes
1 week	1
3 weeks	2
2 months	3
4 months	5
6 months	5
7 months	4
8 months	3
12 months	2
	25 total

Results

Table 1 shows the postoperative survival time together with the number of eyes examined. We operated on 16 rabbits, mostly one eye at a time. The animal with one week survival time suddenly died of unknown causes; the results of the study on this specimen were therefore not taken into account.

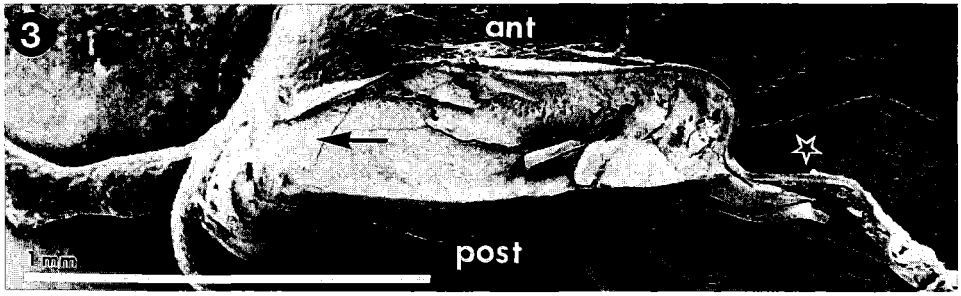
Soemmerring's ring was found in all dissected eyes (Fig 1a, and b). No clear-cut Elschnig's pearls were observed. In most cases remnants of pigment-containing cells were found on the outside of the anterior capsule of the ring, probably derived from the pigment epithelium of the iris (Fig. 2a

and b). In different places in the anterior chamber of the eye (e.g., on the anterior side of the iris), light microscopy showed parts of the dissected anterior capsule, enclosing small amount of acidophilic material. These so-called lentoids of Thiel will not be discussed, as they are beyond the scope of this article.

Three weeks after the operation, the equatorial part of the lens remnants was still rather flat but definitely a ring-like structure had been formed. In the center of the ring the posterior lens capsule was sometimes covered with fibrin-like material (Fig. 1a). In transection, the walls of the ring comsisted of the posterior and anterior capsules, the anterior capsule being thicker than the posterior one (Fig. 3). The material enclosed between the capsules predominantly consisted of lenticular fibers oriented in a regular pattern. The equatorial cap of nucleated fibers showed the configuration of a normal lens bow, i.e., an arrangement of fiber nuclei in a bowlike pattern. (In Figs. 3 and 11a, its site is indicated by an arrow.)

Between 3 weeks and 4 months survival time after the operation, the ring increased in size on cross section. The central part of the ring, formed by the posterior caopsule, proved to be smooth on its vitreal surface. The pupillary surface showed various adherent structures: parts of the dissected anterior capsule, fibroblast-like structures, various fibrillar materials (Figs. 4a and b), and peripherally also the curled-up attachment of the anterior and posterior capsule (Fig 11b, asterisk). In transection, the anterior and posterior capsule of the ring did not show much difference compared with the capsules after 3 weeks survival time. At its inner face the capsule was lined by a monolayer of epithelial cells. The inner face of the posterior capsule was not lined by epithelium except for an accumulation of epithelial cells near the site of fusion between the anterior and posterior capsules. The main difference between the Soemmerring's ring at 3 weeks and 4 months was the increasing loss of regularity in the fiber organization of the latter. The equatorial cap of nucleated fibers was still there but the more central fibers in the ring showed various degrees of degeneration. Normal fibers are hexagonal and are anchored by various cell embrane specializations like interlocking protrusions, ball and socket junctions, undulations, folds, and bends. Most fibers in the center of the Soemmerring's ring became irregular or sometimes square or triangular. The anchoring elements were changed in various ways; often great undulations and distorted interlocking protrusions were found. Sometimes fibers seemed degenerated to such an extent that only a skeleton remained. Some of these normal and abnormal lenticular fibers are shown in Figs. 5-8. Besides the lenticular fibers, also globular amorphous masses were observed at a more central position in the ring. (In Fig. 9, a transitional zone is depicted.)

Between 4 and 12 months survival time, no significant changes in the shape or size of the ring were noted. The rings were 5-7 mm wide and the maximum thickness of the ring was 2.5 mm. The organization of the zonu-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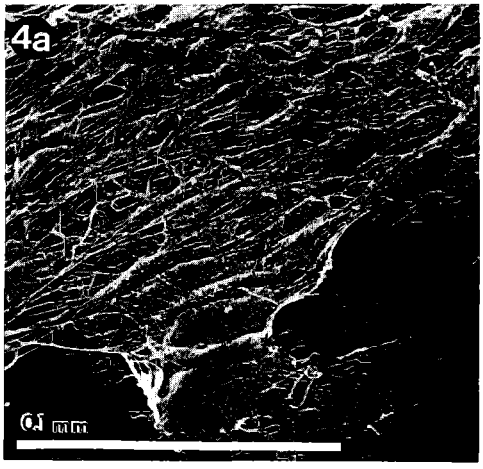
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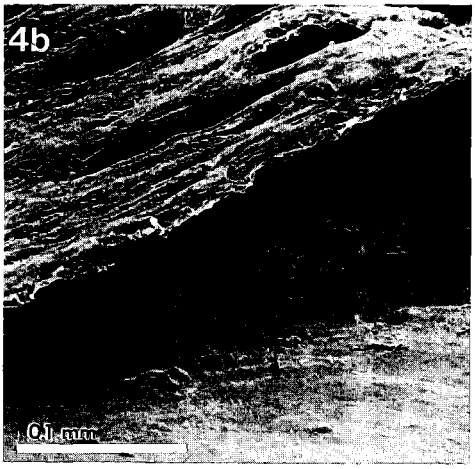
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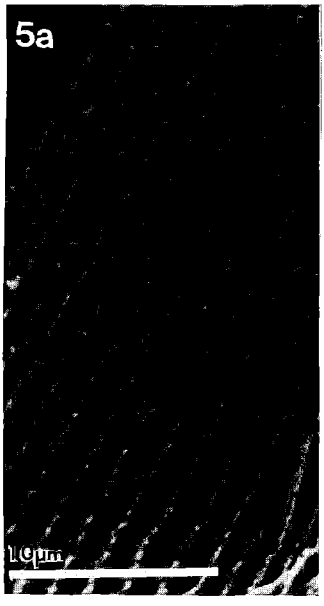
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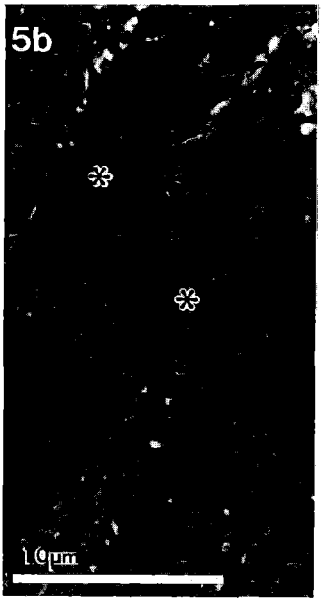
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6
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lar fibers of a specimen after 8 months survival time was studied. Macroscopically and biomicroscopically, the zonular fibers looked normal and scanning electron microscopy also revealed no alterations (Fig. 10). The central part of the capsule showed no difference compared to the specimen with a shorter survival time. In transection, the anterior capsule was thicker than the posterior capsule and was multilayered. This multilayering is shown in Fig. 12. Maximal thickness was found at the site where the anterior capsule was approaching the curved site of fusion with the posterior capsule (Fig. 11). The capsule itself had a granular appearance (Fig. 12).

At its inner surface the anterior capsule was lined by one layer of epithelium; in some specimens, however, multilayered epithelium was found in some places. The inner face of the posterior capsule rarely had an epithelial lining except near the fusion site of the anterior and posterior capsule (Fig. 11a, open arrow), as had been found already in an earlier postoperative stage. Epithelial cells at this place were present in groups, separated by strands of capsular material. These cells were highly vacuolized, as could be demonstrated by transmission electron microscopy. Two types of epithelial cells could be distinguished (Fig. 13a and b). One type had a lobulated nucleus, containing a lot of marginal, darkly staining heterochromatin. The cytoplasm contained numerous clear vacuoles, large cistern of endoplasmic reticulum, and few mitochondria. The other type of cell contained a smaller nucleus with one or two smaller nucleoli without associated chromatin. Its cytoplasm had a fine granular aspect and only a few vacuoles and cell organelles could be observed. The second type was especially common in and near the site of fusion of the anterior and posterior capsule, but in some places the two types could be found adjacent to each other.

Sometimes transitional forms were found. In transection, the content of the ring was extremely variable, from nearly normal fibers to amorphous, globular masses. Superficially in the equatorial region, the ring was made up by nearly normal fibers, closely packed (Fig. 5a) and with a normal set of anchoring devices, such as ball and sockets and interlocking protrusions (Fig 5b). Sometimes irregularities in the pattern were obvious. In addition, folds and bends of the fiber surface were regularly observed in this region (Fog 6). The numerous lens fiber nuclei were generally oval-shaped and contained lightly staining chromatin and up to three small nucleoli free of associated chromatin, thus resmbling the nucleus of the second type of epithelial cell (Fig. 14). In transection of the ring as a whole, these nucleated fibers were arranged near the equator in a bowlike pattern, the lens bow. A second lens bow was also observed posteriorly from the fusion site of anterior and posterior capsule (Fig. 11a, arrows).

In deeper parts, the fibers became more irregular, often with a flattened outline and more complicated interlocking protrusions (Fig. 8). In some instances, the outer aspect of the lens fibers was degenerated, in some pla-

ces leading to the formation of large empty holes (Fig. 7). These structures probably represent Morgagnian globules. The amorphous structures that may fill a large part of the ring are illustrated in Fig. 9.

Discussion

Since the first description of after-cataract in rabbits by Dietrich in 1824 and somewhat later in man by Soemmerring in 1828, (reviewed by Duke Elder, 1969) many investigators have described the so-called ring of Soemmerring (Werneck, 1833; Textor, 1842; Wessely, 1910; Poos, 1931; Cowan and Fry, 1937; Binder et al. 1961; Smith et al. 1982) using mostly biomicroscopic and light microscopic methods. More recently, McDonald et al. (1974) have studied the development of after-cataract in the rabbit using transmission electron microscopy and ^{3}H-thymidin autoradiography as well. In addition to the formation of Soemmerring's ring, several have observed partial or complete regeneration of lenses after extracapsular extraction in the rabbit and other species (Cocteau and Leroy-d'Etiolles 1827); Gonin 1896; Stone 1958). Binder et al. (1961) have carried out a detailed study on this subject, concluding that the degree of degeneration depends on the extensiveness of adhesions between the anterior and posterior capsule during wound healing. Fibrin is thought to play a role in this process. A consistent observation in human after-cataract is the presence of so-called Elschnig's pearls. They have been described in detail by Cowan and Fry (1937), Hiles and Johnson (1980), and by McDonnell et al. (1983) in man. Roy and Hanna (1975) mention their formation in the rabbit.

In the present study we consistendly found the formation of Soemmerring's rings. On only one occasion did we observe a partially intact lens. At enucleation after 4 months survival time, half of the lens was present, either due to regeneration or incomplete extraction. The other part of the lens was occluded by extensive adhesion of the lens remnants with the iris. The low incidence of regeneration in our study contrasts with the observation of Binder et al (1961). However, they did not remove the anterior capsule, whereas in our study a large part of the anterior capsule was dissected, as is also common practice in human extracapsular cataract extraction.

In rabbit, constant dilation of the pupil is not easily obtained and, therefore, complete removal of the anterior capsule is not as easy as in man. However, as much anterior capsule as possible was removed in this experiment. This procedure may induce adhesions between the posterior capsule and the remnants of the anterior capsule. Moreover, anterior capsule removal may induce more abundant wound healing and fibrin deposition, which seems to arrest regeneration (Binder et al. 1961).

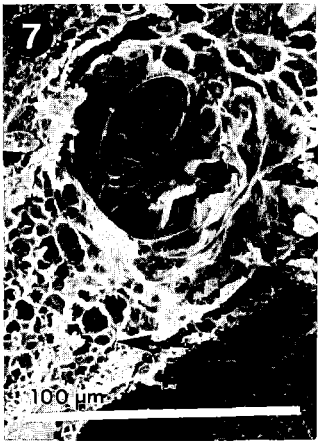
Regarding the formation of Elschnig's pearls, on biomicroscopy only

one eye showed these pearls on the pupillary face of the posterior capsule. However, postmortem inspection did not substantiate this observation. According to Duke-Elder (1969), Elschnig's pearls are derived from subcapsular epithelial cells that escape from the ring and are aberrantly deposited on the posterior capsule. Their absence in our study, and the fact that they are found in rabbit in one study only (Roy and Hanna, 1974), may indicate that in this species the adhesion between the anterior and posterior capsule is rather firm, leaving little space for escaping epithelial cells. The common observation of Elschnig's pearls in man probably indicates that the adhesion of the capsules is less firm in man.

The fibrillar and cellular debris on the pupillary face of the posterior capsule, as found in the present study, confirms the observations of others (Duke-Elder 1986; Smith et al 1982). In contrast with the capsule of the intact lens, the capsule of the ring of Soemmerring is multilayered, as has also been noticed by McDonald et al. (1974). These authors explained this layering by assuming that the metabolism of the epithelial cell changes after lens extraction, most likely by a shift in synthesis of the relative amount of collagen and mucopolysaccharides, the main constituents of the capsule. The ring capsule also seems to be much thicker than normal in some areas, especially in the anterior capsule near the equator (McDonald et al. 1984; this paper).

Prince (1964) has investigated the thickness of the lens capsule in control rabbits and reported that the anterior capsule is much thicker (10-25 um) than the posterior capsule (4-6 um). A maximal anterior thickness of 25 um was found near the equator, which gradually decreased to 10 um in the anterior pole and to 4 um in the posterior pole. Prince made these observations in young rabbits. In the adult rabbit the posterior capsule has about the same thickness, but during its lifetime the anterior capsule can increase in thickness by a factor of three. This local variation in thickness of the capsule and its increase with time makes it difficult to interpret the changes in thickness of the remnants of the anterior capsule. Also, the posterior capsule seemed to have increased in thickness - at least where it was covered at its inner side by epithelial cells. The presence of capsule-producing epithelial cells in this region, as can be deduced from the layered aspect of the capsule, supports this conclusion.

In transection of Soemmerring's ring, an epithelial lining all along the anterior face was observed at the inner side of the capsule. This fully confirms previous observations given in the literature by various authors. At its inner side, the posterior face had an irregular epithelial lining, mainly along the medial half. Epithelial cells on the outer side of the anterior capsule, as mentioned by Cowan (1937) in man, were not found in our rabbits. Light microscopic observations using 5-10 um sections showed that at the equator and also near the fusion site of the anterior and posterior capsule, nucleated fibers were arranged in a configuration resembling a lens bow. This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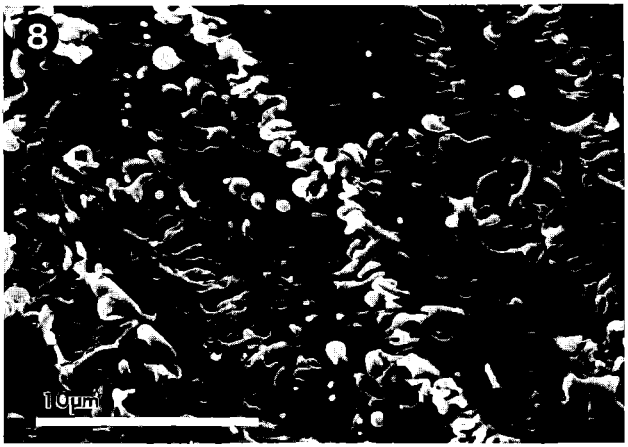
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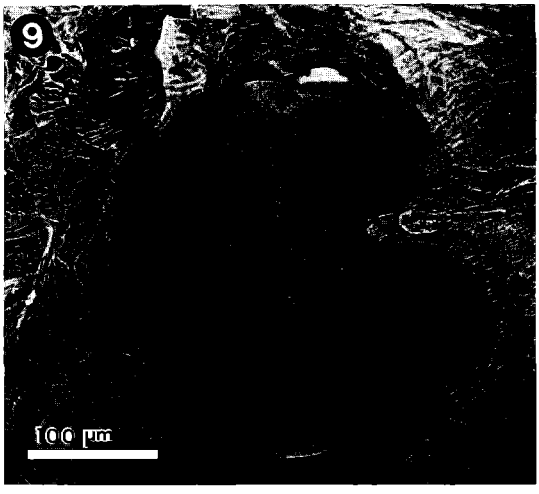
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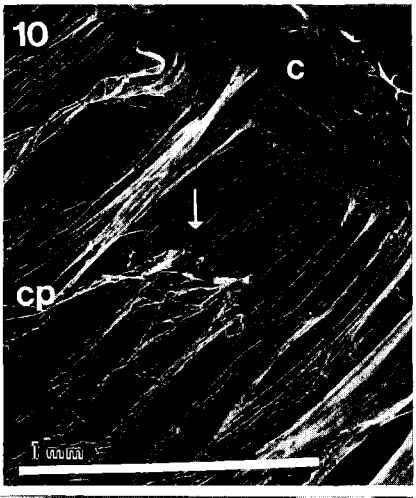
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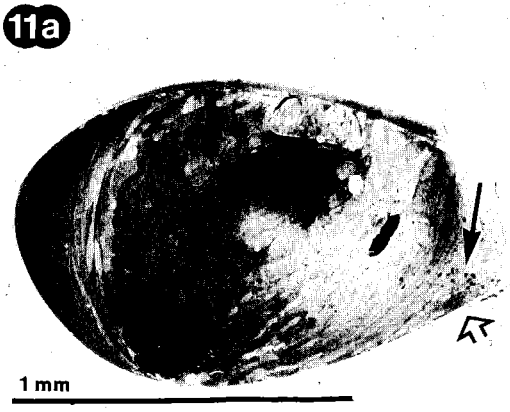
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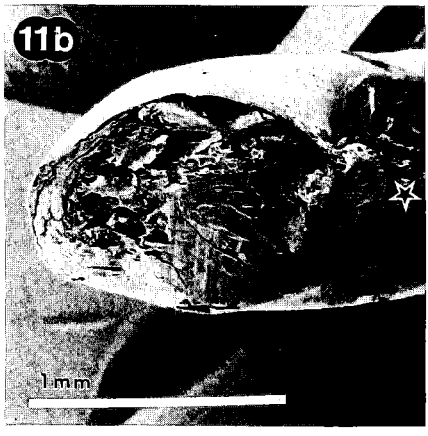
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confirms the observations of Wessely (1910) in man.

Ultrastructurally, two cell types could be distinguished. The first type was characterized by an indented nucleus with numerous patches of chromatin, large cistern of endoplasmic reticulum, numerous clear vacuoles, and a normal set of cell organelles (Fig. 13a). A second cell type was characterized by a round-to-oval nucleus that was indented less, with unfolded chromatin and a clear-cut nucleolus, few cytoplasmic organelles, and a homogenous cytoplasmic matrix (Fig. 13b).

Transitional forms occurred between the first and second epithelial cell type. Some of the cells of the second type strongly resembled the young lens fibers seen in the lens bow region of intact lenses. These two distinct cell types, with comparable structural characteristics, have also been observed in McDonald (1974). This distinction between two cell types, one of which sometimes resembled newly formed fibers, indicated that the epithelial cells left behind after the extracapsular extraction were able to differentiate. From the fact that they are also able to divide and synthesize capsular material (McDonald 1974), it can be concluded that the epithelial cells retain their vital functions after the extracapsular lens extraction. A new observation in the present paper is that the superficial fibers in the ring of Soemmerring bordering the equatorial region were relatively normal and exhibited, in an orderly fashion, the mutual anchoring devices. These anchoring devices have been described in detail in control rabbits (Willekens and Vrensen, (1981). More to the center in Soemmerring's ring appeared the ultrastructure of degenerated fibers and globular amorphous structures. The disturbed structures were mostly present in the center of the transsected ring or away from the differentiating, newly formed lens fibers. This probably indicates that normal lens fibers, when they are pushed to the center due to the addition of new fibers, become disturbed and degenerate (for an illustration of this phenomenon see Fig. 9).

Extracapsular extraction of lenses in the rabbit leads to the formation of rings of Soemmerring, which gradually increase in thickness during the first three postoperative months. The epithelial lining of the capsule seems to consist of vital cells, as can be deduced from the fact that they are able to divide, to lay down new capsular material (McDonald 1974), and to differentiate into relatively normal fibers, with mutual interconnections, as in normal control lenses (this study). The normal continuous outgrowth of the newly formed fibers is obstructed, most likely due to adhesions of the anterior and posterior capsule at the interior margin of the ring. This results in degeneration of these originally normal fibers, and finally, to the formation of amorphous masses and Morgagnian globules. The absence of clear-cut Elschnig's pearls on the pupillary face of the posterior capsule may indicate that the marginal adhesion of anterior and posterior capsule is stronger in rabbits than in man.

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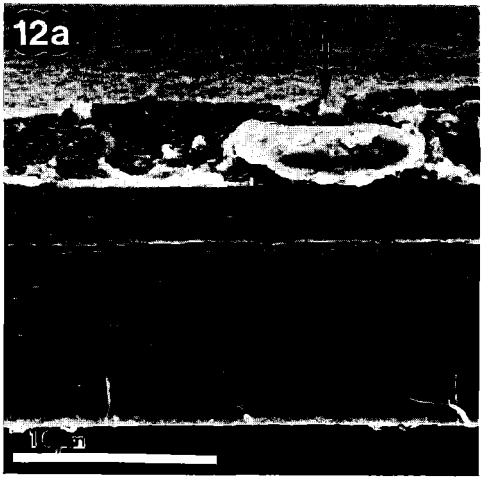
Legends

Fig. 1 a,b Low-power scan of Soemmerring's ring in the rabbit. **a** 3 weeks and **b** 6 months after extracapsular cataract extraction. both pictures illustrate the doughnut-shaped encapsulated lenticular remains in the periphery and the retained posterior capsule in the center. **a** shows the more flattened aspect and central deposition of fibrin at short survival time. **Inset:** Medium-power scan of the fibrin.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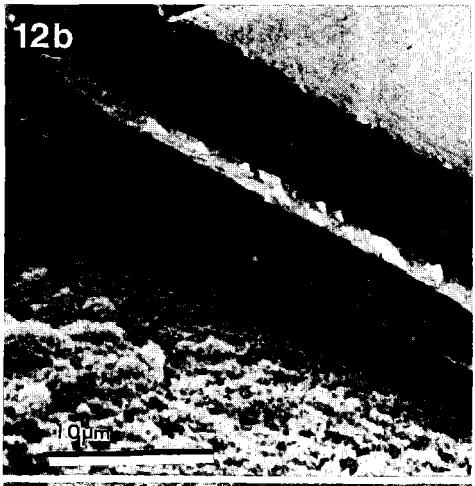
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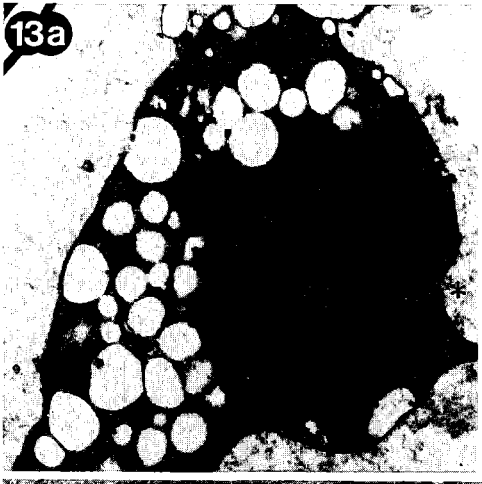
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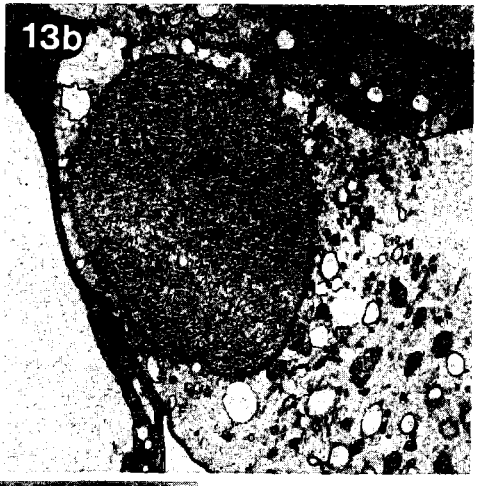
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Fig. 2 a,b Medium-power scan **a** and transmission **b** picture of posterior synechiae on the anterior capsule of Soemmerring's ring. In the transmission picture pigment granules are indicated by **arrows**: the cell membrane is lost, probably due to a preparation artifact. In the scan, numerous globular cells (**arrows**) and fibroblast like cells are adherent to the capsule **c**.

Fig. 3 Medium-power scan of transection of Soemmerring's ring (3 weeks survival time). The walls of the ring are formed by anterior and posterior capsule, which are fused centrally. The curled-up adhesion of the anterior capsule to the posterior capsule is indicated by an **asterisk**. The equatorial cap of nucleated fibers is indicated by an **arrow**.

Fig. 4. a Fibrillar material and fibroblast-like cells are seen on the pupillary surface of the posterior capsule in the center of Soemmerring's ring. In **b**, capsular remains are observed.

Fig. 5. a,b. High resolution picture of normal lenticular fibers found in Soemmerring's ring: **a** illustrates the regular pattern of the fibers; **b** the ball and socket junctions (**asterisks**); the interlocking protrusions (**arrows**).

Fig. 6. High-resolution scan of normal lenticular fibers found in Soemmerring's ring. These fibers exhibit two more types of membrane specializations: undulations and folds and bends. These fibers are found in control rabbit lenses in the lens bow region.

Fig. 7. Medium-power scan of degenerated fibers found in Soemmerring's ring. Besides skeletal fibers (**arrows**) large empty globular structures were observed. These structures probably represent the SEM analogs of Morgagnian globules as seen in light microscopy.

Fig. 8. High resolution scan of lenticular fibers with exuberant large and irregular interlocking protrusions found in Soemmerring's ring. Groups of these fibers were found showing variuos degrees of deterioration.

Fig. 9. Medium-power scan of the center of a transection of Soemmerring's ring. The upper part of the picture shows the more peripheral lenticular fibers (**F**); the lower part exhibits amorphous structures (**A**).

Fig. 10. Medium-power scan of the zonular fiber organization of Soemmerring's ring. The ruptured fibers are artifactual. **c**: capsule of the ring; **cp**: ciliary process.

Fig. 11. a,b. Soemmerring's ring in transection (7 months survival time). **a** illustrates the thickness of the anterior capsule in light microscopy. The

black arrows indicate nucleated fibers arranged in a configuration resembling a lens bow. These configurations are seen at the equator and posteriorly from the fusion site of the anterior capsule to the posterior capsule. The **open arrow** indicates the place where epithelium was found under the posterior capsule. The **asterisk** indicates the fusion site of anterior and posterior capsule.

Fig. 12. High-resolution scan of the anterior capsule after 8 months survival time. The multilayering is clearly demonstrated.
In this picture the subcapsular epithelium is seen from above. The **arrows** indicate the protruding nuclei.

Fig. 13. a,b Transmission picture of the two types of subcapsular epithelial cells. **a** illustrates the cell type with numerous vacuoles (**V**), large cisterns of endoplasmic reticulum (**asterisk**) and a lobulated nucleus (**N**) with marginal heterochromatin. **b** illustrates the cell type with a fine granular cytoplasm (**C**), fewer and smaller vacuoles (**V**) and a smaller nucleus with nucleolus (**N**).

Fig. 14. Transmission picture of one of the nucleated lens fibers. the nucleus is oval-shaped and contains lightly stained chromatin with two nucleoli (**n**) without associated chromatin, thus resembling the nucleus of the second type of epithelial cell.

2.2. The proteinaceous coating and cytology of implant lenses in rabbits (American Journal of Ophthalmology 102: 750-758, 1986).

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Key words: Implant cytology, posterior chamber lenses, macrophages, fibronectine, rabbits.

Summary

We performed extracapsular lens extraction with implantation of a J-loop posterior chamber lens in 14 rabbit eyes. Postoperatively the animals were examined by slit lamp. They were killed after varying survival times of up to 12 weeks, and the implants were examined by scanning electron microscopy.

Three days after the operation a thin amorphous coating that did not consist of collagen was found covering all implants. Three cell types were present on the coating: macrophages, leukocytes and flattened giant cells. This coating resembled morphologically the fibronectin coating on intraocular lenses in vitro.

Introduction

More than 500,000 intraocular lenses are implanted per year in the United States [1]. The most widely used implant materials (polymethylmethacrylate, polypropylene and polyamide), show a generally good biocompatibility [2].

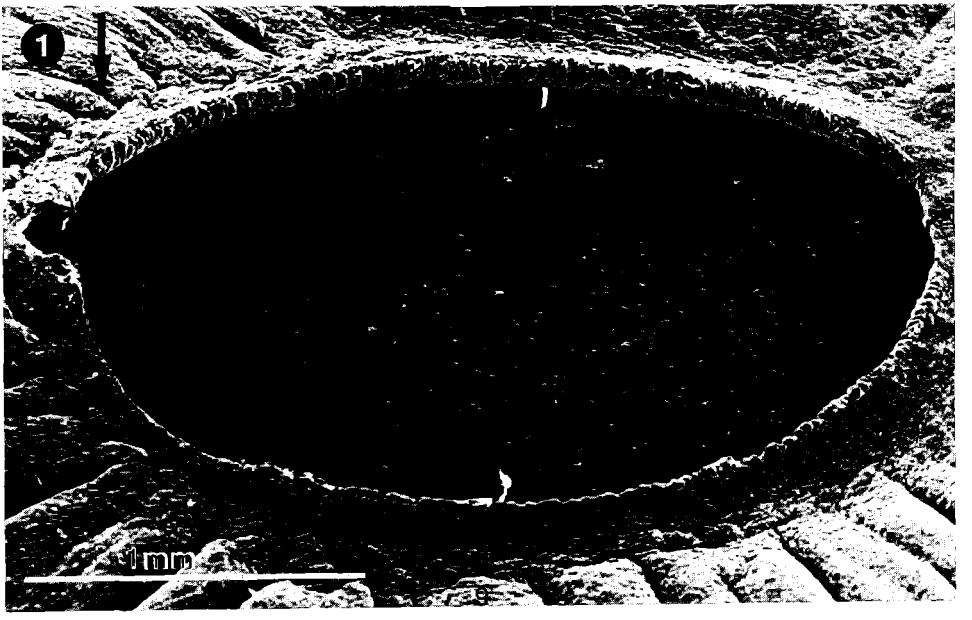
The question has been raised why these artificial materials do not induce a destructive foreign body reaction [3]. However, a mild reaction of the host to the implanted lens has been described in humans. [4-7]

To investigate this phenomenon systematically we used an animal model. We implanted posterior chamber intraocular lenses in 14 rabbits. The animals were killed according to plan after varying survival times. Histologic findings on the surface of the implant were studied by scanning electron microscopy to determine the sequence of events in the reaction of the host to the implant.

Material and Methods.

Fourteen sodium hydroxide sterilized polypropylene looped polymethylmethacrylate lenses (J-loop type) were implanted after extracapsular lens extraction in the eyes of adult Dutch pigmented rabbits. Preoperatively the rabbits were treated for three days with 0,5% indomethacin eyedrops three times a day to prevent fibrin accumulation during intraocular surgery. During the two hours before surgery 10% phenylephrine, 1% cyclopentolate, 1% tropicamide and 0.5% indomethacine eye drops were administered every 15 minutes to dilate the pupils. Shortly before surgery the animals were sedated by intramuscular injection of 2 ml. of chlorpromazine (5 mg/ml) and anesthetized by slow injection of 2-4 ml of pentobarbital sodium (60 mg/ml) in the marginal ear vein. Analgesia was improved by subconjunctival injection of 1-2 ml of prilocaine hydrochloride (20 mg/ml). All operations were performed under a microscope with co-axial illumination according to standards used in human cataract surgery by one of us (J.H.P.). Both eyes of each animal were operated on.

A bent, disposible 27-gauge needle on a syringe filled with air was stabbed through the cornea without prior incision. With this needle the anterior lens capsule was opened along the pupillary border. A 150-160 degree corneal incision was made. Two corneal sutures were placed for security and were looped aside. The anterior capsule was grasped with a pair of Vogt capsule forceps. The lens nucleus was easily washed out by positive vitreous pressure with an olive cannula and Ringer's solution. However, mild expression was necessary in some cases. The residual cortical material was irrigated using a flat cannula, although hyperemia of the iris and narrowing of the pupil prevented complete irrigation. The anterior chamber was then restored by injection of 1 ml of sodiumhyaluronate. Insertion forceps were used to grasp the superior haptic of the intraocular lens, and the inferior haptic was slipped into place in the inferior capsular fornix. By rotating the lens the superior haptic was brought into the superior capsular fornix. To prevent bleeding and excessive fibrin formation no peripheral iridectomy was performed. The corneal incision was closed in one layer,


1
1 mm


2
10 µm

using 10.0 nylon.

No postoperative treatment was given. During the first postoperative day we observed a mild to severe fibrinous reaction in the anterior chamber and the occurence of pigmented precipitates on the optic part of the implant. The dissolution of the fibrin and the development of cellular elements on the implant was tracked by slit-lamp examination.

After survival times varying from three days to 12 weeks the animals were injected with an overdose of pentobarbital sodium (Table). The eyes were immediately enucleated and placed in a cacodylate buffered glutaraldehyde/formaldehyde fixative[8]. To improve penetration of the fixative the anterior chamber was opened by a corneal incision. After one week of fixation the anterior segments were thoroughly rinsed in cacodylate buffer, dehydrated in a graded series of ethanols and critical point dried with CO_2.[9] The specimens were glued on specimen stubs with conductive carbon cement and coated with approximately 7 nm of gold. The specimens were examined by scanning electron microscopy using a secondary electron detector.

Additional experiments with three new, wet-pack sterilized J-loop intraocular lenses were performed. One lens was incubated at 37 C for 24 hr in saline and two lenses were incubated seperately at 37 C for 24 hr in a solution of 1,000 microgr/ml of fibronectin. After fixation in cacodylate buffered glutaraldehyde/formaldehyde fixative [8] the lenses were prepared for scanning electron microscopy as described above.

Results

On the first postoperative day slit-lamp examination through the somewhat hazy cornea disclosed varying amounts of fibrin together with a moderate number of pigmented deposits on the anterior surface of the lens. During the first two weeks postoperatively most of the macroscopically visible fibrin disappeared and more pigmented deposits could be seen on the optic. The iris showed a mild to severe hyperemia, and in three cases pupillary capture occurred. In one case the fibrin reaction was severe and an irregular mass almost filled the anterior chamber. Since this animal was to be killed three days after the operation, we did not wait for the dissolution of the fibrin. The contralateral eye of this animal showed almost no fibrin reaction.

As the survival time increased, the size of the pigmented deposits increased. The maximum number of deposits (ten to 15) was present about three weeks after the operation and could be seen on the anterior side of the implant. Dissection of the eyes showed that in all cases both loops of the intraocular lens were placed in the capsular bag and that the peripheral

cortical remnants were enclosed by the anterior capsular flap and the posterior capsule, forming a Soemmerring's ring.

Scanning electron microscopy disclosed the ultrastructure of the pigmented deposits on the anterior surface of the lens (Fig. 1).
Two intraocular lenses with an implantation time of three days were studied. On one, a dense mass of fibrin and a number of leukocytes was present. The fibrin mass prevented further inspection of the lens surface. The other specimen showed less fibrin. On the surface of this lens a thin, wrinkled coating was found, which was accidentally torn at several places (Fig 2). The thickness of this coating did not exceed 1 um. On this coating numerous cells were distributed over the entire surface. More than hundred cells were identified, ranging in size from 10 to 100 um . Most of the cells were flat, had a round to oval outline (maximal diameter, 10 um), and were covered with villi (Fig. 2 and 3, arrows). Only few large flat cells were found with diameters up to 100 um (Fig 3, asterisk).

The findings one week postoperatively were similar to the findings three days postoperatively. However, three different types of cells were identified. The first type of cells, approximately 5 um in diameter, was spherical and covered with villi (lymfocytes) (Fig 4, arrows). The second type of cells were round and flat with a central elevation and a diameter between 10-30 um. They were probably activated macrophages (Fig 4). The third cell type was large, irregularly shaped and had a maximal diameter of 150 um (Fig 5). The two specimens studied here were both covered with several hundreds of cells of which only 10 per cent was of the third type. The remaining 90% consisted of about equal numbers of the first and second types of cells. There was still some fibrin present (Fig 5).

Two weeks postoperatively the thin coating on the lens was still present together with some fibrin and numerous cells of the three types described above. However, the large cells were even larger. Flattened cells, covered with microvilli, and over 300 um wide, were found near the holes of the optic part of the intraocular lens that are used for manipulation during surgery (Fig 6). Other ceels. more than 100 um in diameter, were round and showed a central elevation. Four weeks postoperatively the coating on the lens was still present and in some cases some fibrin was found. The cell population was essentially the same as that found three weeks postoperatively, including the huge flattened cells. Few huge cells were seen in each specimen, but their size exceeded 400 um. As can be seen in Fig 7 they had growing processes and were incomplete in covering the corresponding surface area.

Only one specimen was examined by scanning electron microscopy after 12 weeks survival time. The coating on the implants was still present. There were fewer cells on the surface of the lens and most of them were found in the periphery. The center of the optic was almost free of cells. In the periphery fibrin was found together with leukocytes. Large cells, excee-

ding 350 um in size, were found near the place of implantation of the haptics (Fig 8) and in and near the manipulation holes.

The other specimen with 12 weeks survival time was used for experiments concerning the nature of the thin coating on the lens. The implant was dissected from the eye immediately after death and divided into three parts: one part was treated with collagenase, one part with trypsin and one part with cationized ferritine. Scanning electron microscopy of these parts disclosed a coating on the collagenase-treated part, comparable to that on untreated lenses, and the absence of this coating on the trypsin-treated part. Without gold-coating and with the use of a low accelerating voltage the cationized ferritin treated part of the lens showed a thickened layer of electron conducting material, indicating the presence of iron bound to the surface of the lens.

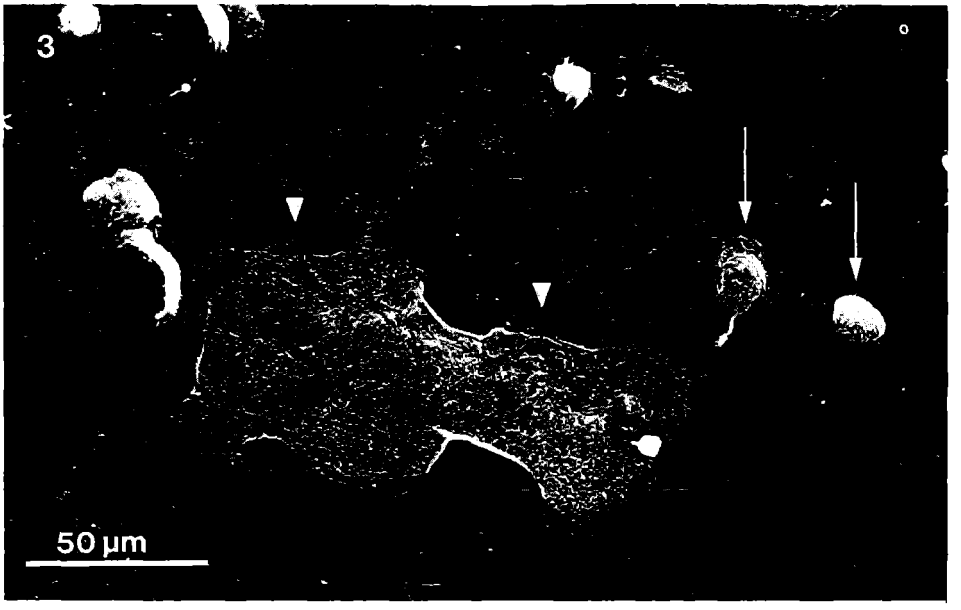
Scanning electron microscopy of the unused intraocular lens incubated at 37 C for 24 hr in saline disclosed a clear surface without any coating. Examination of the two intraocular lenses incubated seperately in a solution of fibronectin (1000 ugr/ml) at the same temperature and for the same period of time, showed a thin, wrinkled coating resembling the coating found on the rabbit implants (Fig 9).

Table
Number of rabbit eyes implanted with intraocular lenses and their survival times

no. of eyes	survival time
2	3 days
2	1 wk
2	2 wks
6	4 wks
2	12 wks

Discussion

Experimental surgery, performed in rabbits, has some major differences when compared with human surgery. The fibrin accumulation in rabbits during intraocular surgery is well known and has no counterpart in humans. However, the reaction described in this study might be applicable to humans since pigmented deposits, cellular elements, and membranes have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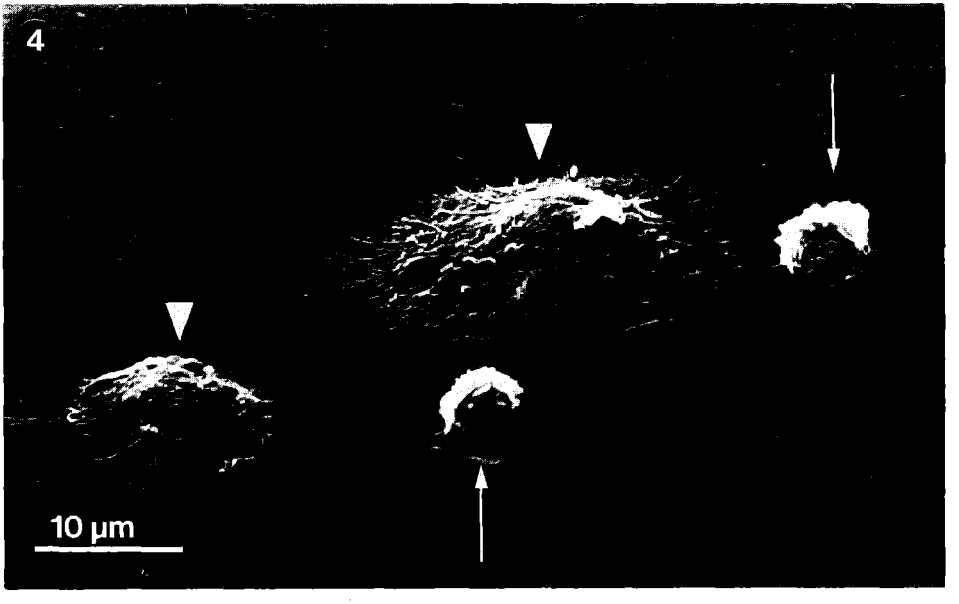
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been frequently reported findings in human [3-7].

As discussed by various authors,[4-7] the implantation of an intraocular lens in humans causes a limited foreign body reaction. Wolter[5-7] described a thin proteinaceous layer with numerous cells on the surface of intraocular lenses obtained from humans postmortem or after surgical removal.

The membranes on intraocular lenses described by Wolter are partly cellular with an acellular proteinaceous component that fills the interspaces[5]. These human specimens had a longer implantation time than the lenses in our study. The cells observed were primarily macrophages or differentiation products of macrophages, such as epitheloid cells and giant cells. Almost all of these cells contained pigment granules in their cytoplasm. These findings were confirmed by Sievers and Von Domarus[4]. In 1986, the scanning electron miroscopical finding of a thin wrinkled coating on the intraocular lens was described in human material[10].

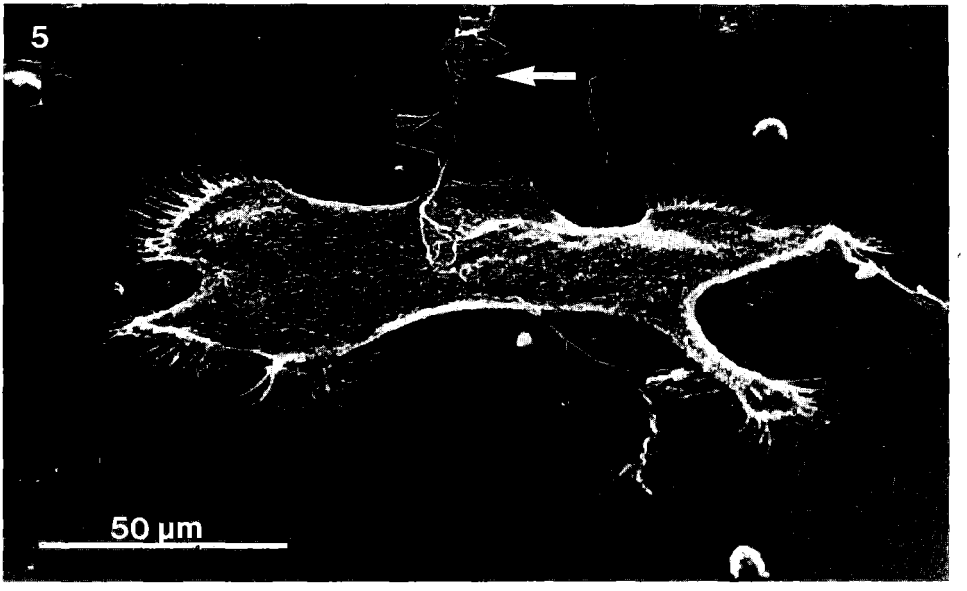
The three cell types found in this study correspond to those previously reported. The smallest cells are apparently leukocytes, present as a result of the wound reaction. The larger, round cells with the central elevation are macrophages, and the third cell type consists of either epitheloid cells or giant cells. Differentiation between these two latter types is difficult by scanning electron microscopy.

The most remarkable finding in our study is the rapid appearance (three days postoperatively) of a thin coating on the lens. Ohara[3] reported in vivo large pigmented deposits and fine pigment particles on the surfaces of an implanted lens in humans from the first postoperative day in an uncomplicated case.

To determine the nature of this coating we treated it with collagenase, trypsin and ferritin. Since collagenase did not harm the coating, the coating was not made of collagen. Trypsin, a protein digesting enzyme, destroyed the coating. Ferritin, which binds to acid groups of proteins, did bind to the coating. The coating must, therefore, consist of a protein with acid binding areas.

We suspected that the coating might consist of plasma fibronectin. Fibronectin is a large glycoprotein that exists in both a cellular form and a plasma form[11]. The cellular form is the major cell surface glycoprotein of many fibroblastic cell lines.[12] The plasma form of fibronectin has a lower molecular weight and is an extracellular protein. It has been demonstrated to mediate several cellular functions, namely cell attachment to substrates,[13] maintenance of cellular structure,[14] and non-immune opsonisation.[15] Polymethylmethacrylate has been shown to bind and surface-activate fibronectin,[11] making it a potentially suitable substrate for fibronectin-mediated cell adhesion. Fibronectin can be released in wound reaction and is known to be produced by macrophages.[16]

In this study we show that plasma fibronectin produces in vitro a morphologically identical coating on intraocular lenses as the coating found


5
50 µm


6
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experimentally in vivo in the rabbit. This observation supports the hypothesis that, shortly after surgery, plasma fibronectin is released in the aqueous and binds to the polymethylmethacrylate of the lens optic. Biochemical analysis of the thin coating on intraocular lenses will be necessary to proof this hypothesis.

To our knowledge, the presence of fibronectin in rabbits has not been previously reported and it might be an important contributor to cell growth on intraocular lenses It is known to promote cell attachment and spreading. Fibronectin might contribute to the final acceptance of the implant by the eye.

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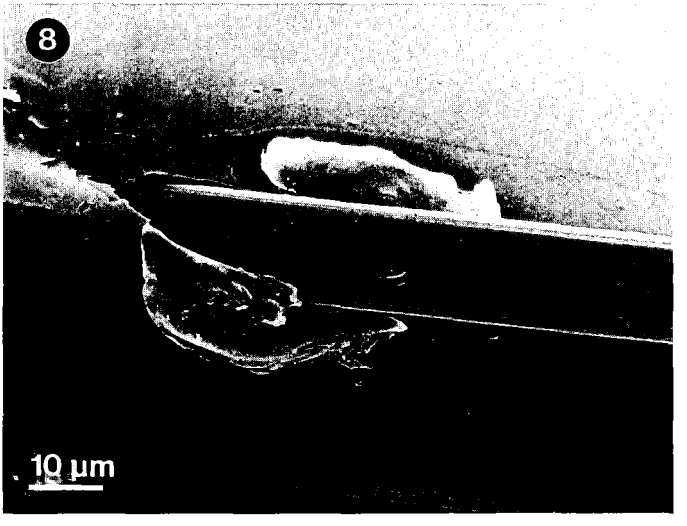
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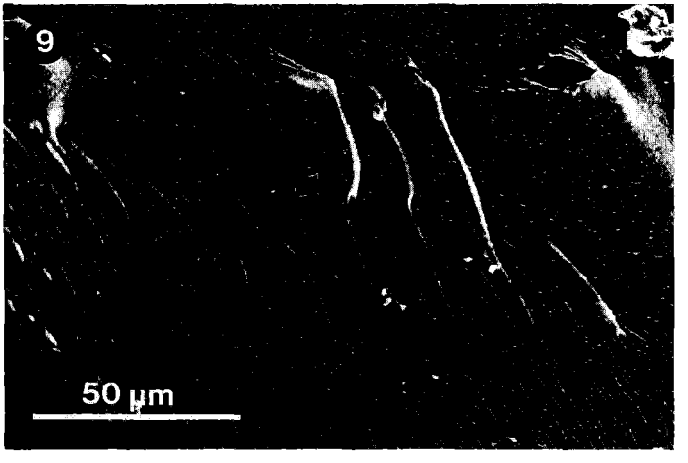
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Legends to the figures

Fig. 1. (Kappelhof and associates) By scanning electron microscopy, at one week survival time, anterior view of posterior chamber lens in the rabbit eye with the cornea dissected. Cells on the anterior surface are visible. The iris is indicated by an arrow. (41x)

Fig. 2. (Kappelhof and associates) At three days survival time, a thin, amorphous coating, accidentally torn at several places (arrowheads) was found on the anterior surface of each implanted intraocular lens. Cells were found

on the coating (arrow) (680x).

Fig. 3. (Kappelhof and associates) At three days survival time a small number of large cells with a diameter up to 100 um were found on the anterior surface of the implant (arrowheads). The arrows indicate the prevalent, smaller cell type. (442x)

Fig. 4. (Kappelhof and associates) On the surface of the implant at one week survival time different cell types could be distinguished. The smallest cell type, about 5 um in diameter, is indicated by arrows. The larger cell type, indicated by an arrowhead, was round and flat with a central elevation and a diameter between 10-30 um. (1770x)

Fig. 5. (Kappelhof and associates) At one week survival time a small number of huge cells was found on the anterior surface of the implant, representing the third identifiable cell type. The arrow shows the location of fibrin (600x).

Fig. 6. (Kappelhof and associates) At two weeks survival time some large cellular elements were found near the manipulation holes of the implant. They were flat, covered with microvilli, and over 300 um wide. (250x)

Fig. 7. (Kappelhof and associates) One of the round, large cells with a central elevation (arrow) found on the anterior surface of the implant at two weeks survival time. (570x)

Fig. 8. (Kappelhof and associates) Some large cellular elements were found near the site of implantation of the haptics at 12 weeks survival time. (90x)

Fig. 9. (Kappelhof and associates) An unused intraocular lens was placed in an aqueous solution of fibronectin (1000 ugr/ml) for 24 hours. Scanning electron microscopy disclosed the presence of a thin, amorphous coating resembling the coating found in vivo as seen in Fig 2. (500x)

3. The anterior lens capsule in man.

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Introduction

The lens capsule is regarded as a tremendously hypertrophied basement membrane surrounding the lens mass 1). This lens mass consists of epithelial cells and their derivatives, the lenticular fibers. The posterior capsule directly borders the cortical lenticular fibers while the anterior capsule is lined at its inner side with epithelial cells.
In extracapsular cataract extraction the anterior capsule is partly removed prior to extraction of the lens nucleus. During this removal a varying degree of resistance of the tissue was noticed by several surgeons. It was suggested that this resistance indicates structural differences in the anterior capsule which might be linked with the cause of cataract formation. There is for example a clinical impression that the lens capsule is much more difficult to open after a previous attack of uveitis. In order to elucidate this problem I studied ultrastructurally anterior capsular flaps removed during extracapsular cataract extraction.

Material and methods

Extracapsular cataract extraction was performed in 35 patients. The age ranged from 11 to 91 years. They were operated on because of senile or congenital cataract. In one case the cataract had been found in a patient with Goldmann-Favre disease, a hereditary vitreoretinal degenerative disorder.

The surgical procedure in removal of the anterior capsular flap was in all cases identical. The cornea was perforated with a hooked needle with which the anterior lens capsule was opened. After making a limbal incision the anterior capsular flap was grasped by forceps and removed from the anterior chamber. Peroperatively the capsule fragments were immersed in a glutaraldehyde-formaldehyde fixative (2) and stored for at least three days at four degrees centigrade with a maximum of two months (2).

Subsequently twenty-four anterior capsular flaps were thoroughly rinsed in cacodylate buffer, dehydrated in a graded series of ethanols and critical point dried with CO . The specimens were glued on specimen mounts with conductive carbon cement and subsequently gold-coated. They were studied in a Philips SEM 505 scanning electron microscope using a secondary electron detector. Twelve specimens were used for thickness measurements , measuring perpendicular to the electron beam.
Four specimens were postfixed with osmiumtetroxide and, after dehydration with ethanol, embedded in Epon 812. Semithin and ultrathin sections were cut and stained with toluidine blue and uranyl
acetate/lead citrate respectively. The semithin sections were used for light microscopical measurement of the thickness of the anterior capsule. This was done by cutting the capsule fragments perpendicular to the capsule surface and measuring these sections with a micrometer. The ultrathin sections were studied in a Philips EM 201 electron microscope.
Seven specimens were cut in two halves. One part was studied by scanning, one part by transmission electron microscopy.


1
100 μm


2


3

Results

On arrival in the laboratory the anterior capsular flaps showed to be curled up, as could be expected given the known elasticity of the capsule 3).
The light microscopy of cross-sections of the capsules showed a thickness which varied with age and with the location of measurement (Table 1). Measured values ranged between 9.2 micrometer in a 72-year old patient (minimum) and 39 micrometer in a 75 year old patient (maximum). Thickness showed a tendency to increase with age but this was statistically insignificant.
Measurements of the thickness by scanning electron microscopy yielded always smaller values, ranging from 5 micrometer in a 11-year old individual (minimum) to 14 micrometer in three individuals aged 54, 82 and 91 years. In some very small specimens only one measurement could be performed, in larger specimens up to five locations were measured. These results are summarized in Table 2.
Scanning electron microscopy gave a three-dimensional view of the ultrastructure of the capsule fragments. The capsules were curled up, so that the inner side, covered with epithelium, was facing outwards (Fig. 1). This means that the surface exposed to the electron beam was always covered with epithelial cells or their remnants. Varying amounts of cortical fibers were found, indicating that accidentally cortical material had been removed together with the anterior capsule (Fig. 1). In a few cases erythrocytes were found.
In cross-section the capsule mostly had a homogenous appearance with large longitudinal grooves (Fig. 2). In some specimens a non-discrete bilayering was visible (Fig. 3).
Transmission electron microscopy showed the capsule to be homogenously fine granular in appearance . The capsule of the patient with Goldmann-Favre disease showed discrete fibrillar areas (Fig. 4).
The epithelium as seen in scanning electron microscope had an irregular appearance. Some cells were swollen, some had been distorted. Many cells had swollen nuclei, as can be seen in Fig. 3. Transmission electron microscopy showed many cells with normal cellular and nuclear membranes and cell organelles (Fig. 5) but also cells with ruptured membranes and swollen or distorted cell organelles (Fig. 6). In addition, epithelial cells with electron dense cytoplasm were observed (Fig. 5).

Discussion

The thickness of the human lens capsule exhibits local variations and varies with the age of the individual and with several ophthalmological or systemic disorders (3, 4). The lens capsule of a healthy individual is thinnest at the posterior pole, and on both the anterior and posterior surfaces there is a circular zone of maximal thickness running concentrically with the equator a short distance axial to the insertion of the zonular fibers (Fig. 7).

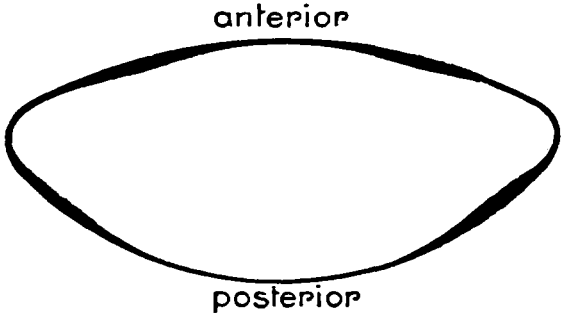

Fig. 7 The lens capsule constucted from post mortem specimens (3).

The thickness of the lens capsule increases during life but tends to become thinner in the old age (4). Measurements in literature give values ranging from two micrometers at the posterior pole to 23 micrometers at the anterior zone of maximal thickness (3). The thickness of the anterior capsule in the adult was reported to range between 14 and 21 micrometers (3,4). It remains unclear how these measurements, mostly dating from the beginning of this century, have been performed. The fact that the light microscopical measurements in this study exhibit larger values might be explained by differences in fixation techniques. Another possibility is that the surgical rupturing disturbs the epithelial pumping system and that the macromolecules attract water.
The much smaller values of the scanning electron microscopy measurements probably reflect the shrinkage of the capsule during the dehydration and the critical point drying procedures. The fact that values obtained by

different methods have a great variation indicates that measurements of capsule thickness especially when ruptured during surgery have to be regarded with suspicion.
The morphological structure of the capsules as found in this study is rather homogenous. Only in the patient with Goldmann-Favre disease I found patches of medium-course filaments in a fine granular matrix (Fig. 4). Such fibrillar groups are often found as attachment sites for zonular fibers but these are lying much more superficially. In addition the border between epithelium and capsule which was straight in all other specimens was irregular in this subject. Whether this capsular aberration is related to the etiology of this disease needs further investigation.
The bilayering and the longitudinal grooves as found in scanning could not be found by transmission electron microscopy. They might as well be an artifact, caused by shrinkage. The transmission electron microscopical findings correspond well with literature 5,6).
The main question which initiated this study cannot be answered equivocally. The variation of capsule thickness with the location on the lens and with age could be one factor explaining the difference in strength. The accidental removal of cortical fibers by the grasping forceps is another factor which certainly increases the resistance of the tissue. A difference in macromolecular composition in the cataractous lens cannot be ruled out because the used methods give no information about this. material while grasping the anterior capsular flap by forceps.

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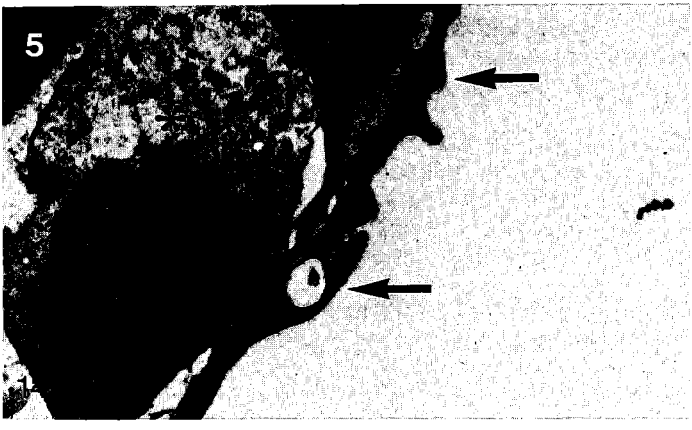
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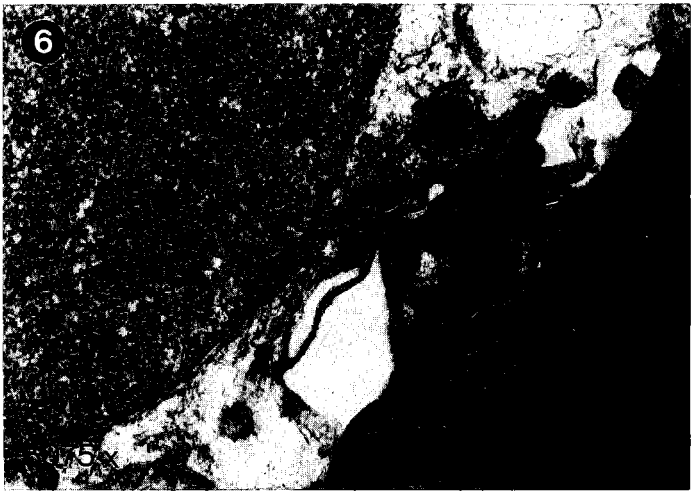
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Figures

Fig 1: Scanning electron microscopy of the anterior capsular flap showing the folded capsule with the subcapsular epithelium (arrowheads) and some swollen and distorted cortical fibers (arrows) of a 60-year old male patient operated for senile cataract (163 X).

Fig 2: A cross-fracture of the anterior capsular flap of the cataractous lens of a 68-year old male patient showing a faintly visible bilayering (arrow). The convex side of the capsule is covered with epithelial cells. At two sites the fracture plane did expose the nuclei (3860 X).

Fig 3: Epithelial cells with swollen nuclei (arrows) are covering this capsule of the cataractous lens of an 82-year old male patient. Longitudinal grooves (arrowheads) are visible in the sectioned anterior capsule (2720 X).

Fig 4: Transmission electron micrograph of subcapsular epithelium (asterisks) with the overlying anterior capsule (between arrowheads) of a 38-year old female patient with cataract and the Goldmann-Favre disease. In this section the nuclei of the epithelial cells are not visible. Two areas of fibrillar material are visible in the capsule (arrows) (6075 X).

Fig 5. Transmission electron micrograph of subcapsular epithelium with the overlying anterior capsule of a 75-year old male patient with senile cataract. Some swollen cortical material is covering the apical side of the epithelial cells (arrows). The striation in the capsule is artifactitious and caused by the cutting of the ultrathin section. Asterisks indicate the subcapsular epithelium. (1490 X).

Fig 6: Transmission electron micrograph of subcapsular epithelium with the anterior capsule (arrow) of an 85-year old female patient. The nuclear membrane is intact but several swollen and distorted cell organelles are visible. (6075 X).

Table 1. Thickness measurements of anterior capsular flaps by light microscopy (N=number of measurements).

Age (yrs)	Thickness in micrometers	N	mean
37	13.8-19.5	14	15.9
72	9.2-15.4	15	12.3
75	16.4-39.0	12	27.4
91	19.5-31.8	12	24.3

Table 2. Thickness measurements of anterior capsular flaps by scanning electron microscopy (N=number of measurements).

Age (yrs)	Thickness in micrometers	N	mean
11	5	1	5
37	6-8	3	7.7
46	6-10	5	8.8
54	14	1	14
60	8-12	5	9.8
67	12.5-13	2	12.8
72	7.5-10	2	8.8
75	7-13	5	8.7
80	8-13	3	10.3
82	14	1	14
91	13-14	3	13.3

4. Extracapsular lens extraction and intraocular lens implantation in man.

4.1. The ring of Soemmerring in man: an ultrastructural study (Graefe's Archive for Clinical and Experimental Ophthalmology 225: 77-83, 1987).

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Note: This study was carried out in the Dept. of Morphology of the Netherlands Ophthalmic Research Institute.

Abstract

The ultrastructure of lens remnants after extracapsular cataract extraction in 11 pseudophakic human eyes is described and illustrated using scanning and transmission electron microscopy. The retained lens material formed a ring-like structure enclosed by posterior and anterior capsule as extensively described in literature and was found to contain dividing and differentiating epithelium. Both normal and degenerating subcapsular lenticular fibres and a central cataractous region were found. The sealing of the anterior capsular flap to the posterior capsule, although rather tight, had failed to prevent epithelial cells from escaping the ring in 9 out of 11 cases. Inflammatory cells near this sealing place and in the ring were found in all three specimens which were examined by transmission electron microscopy.

Introduction

The use of extracapsular cataract extraction (ECCE) as the surgical therapy of first choice for cataract in man merits a more careful study of the fate of lens remnants left in the eye after the operation. It is thought that this

surviving lenticular material causes the opacification of the posterior capsule reported to occur in up to 50 percent of adults within 3-5 years after extracapsular cataract extraction (Apple, 1984). In children almost all of the posterior capsules opacify.

In ECCE the capsular bag, peripherally containing still viable lenticular epithelium, remains in situ. The peripheral lens remnants become organized in a so-called Soemmerring's ring. This structure often is the place where the haptics of an intraocular lens become fixed. The Soemmerring's ring is attached to the ciliary body by the zonular fibers and usually remains stable, although luxation into the anterior chamber has been described (Laibson, 1965, Guha, 1951).

The doughnut-shaped Soemmering's ring light microscopically consists of a variable amount of cortical fibers and proliferating and degenerating epithelial cells encapsulated by the anterior capsular flap that becomes tightly adhered to the posterior capsule (Elschnig, 1911). If one or more of the haptics of an intra-ocular lens are placed in the capsular bag, this process of mutual attachment of the anterior and posterior capsule is supposed to fix the implant.

The aim of this study was to reexamine the development of cataractous changes in Soemmerring's ring and the fate of the lenticular epithelium in human eyes with intraocular lenses using light and electron microscopy.

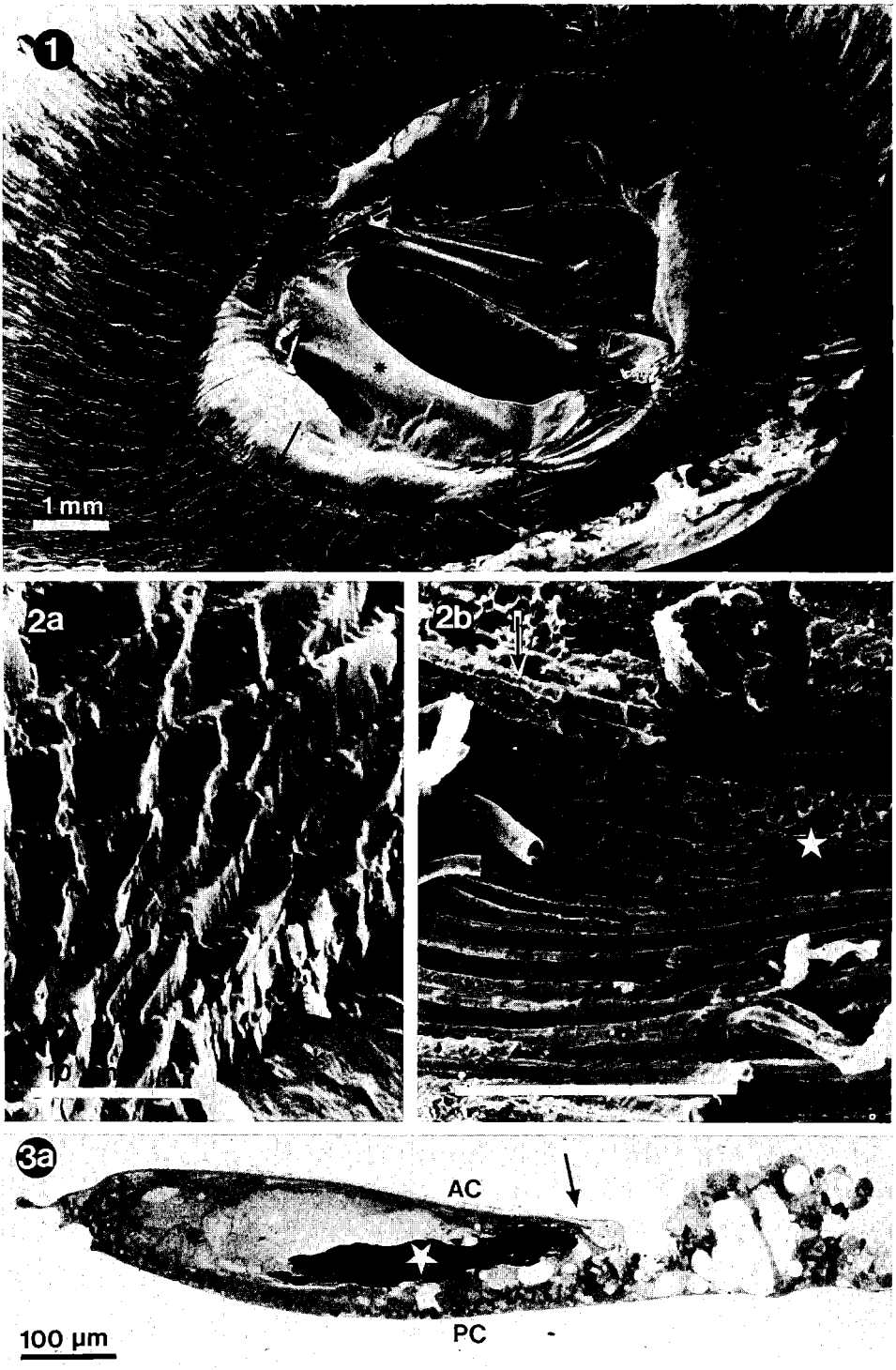
In previous publications the results of a study of the Soemmerring's ring in rabbits were reported (Kappelhof, 1985) and the ultrastructure of Elschnig's pearls in humans was described (Kappelhof, 1986).

Materials and methods

Eleven human autopsy eyes, all treated for senile cataract by extracapsular cataract extraction (ECCE) and all containing intraocular lenses (IOL's), were studied by biomicroscopy, light microscopy (LM), scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The clinical data are summarized in Table 1. The eyes no. 3 and 7 and no. 5 and 6 originated from two patients with bilateral pseudophakia. The eyes 1 and 4 showed biomicroscopically visible Elschnig's pearls, protruding into the pupillary space.

After enucleation nasal and temporal incisions were made in the eye bulb and the eyes were placed in a cacodylate buffered glutaraldehyde/formaldehyde fixative (Peters, 1970). The eyes were stored in this fixative at 4 degrees centigrade for at least one week with a maximum of four weeks. Subsequently the posterior part of the globe and the cornea were dissected. The IOL's were left in situ.

All specimens except no's 4 and 9 were processed for SEM. The specimens were thoroughly rinsed in cacodylate buffer, dehydrated in a graded


1
1 mm
2a
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AC
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series of ethanols and critical point dried with CO_2 (Willekens, 1981). The specimens were glued on SEM specimen mounts with conductive carbon cement, gold-coated and examined in a Philips SEM 505 scanning electron microscope using a secondary electron detector. After inspection the specimens 2,6,and 10 were removed, deliberately fragmented and the newly exposed faces were recoated with gold. Specimen 1 was also fractured and after rehydration fragments of Soemmerring's ring were post-fixed in 1 percent osmium tetroxide and embedded in Epon 812. For LM semithin sections (1 um) of the osmificated material were stained with toluidine blue. Ultrathin sections were stained with uranyl acetate and lead citrate and inspected in a Philips EM 201 transmission electron microscope. Specimens 4 and 9 were dissected directly after aldehyde fixation and parts of the Soemmering's ring were prepared for SEM while other parts were post-fixed in osmium tetroxide, dehydrated in a graded series of ethanols and embedded in Epon-812 for LM and TEM. Half of specimen 9 was used for celloidin embedding. Sections (10 um) of this material were stained with hematoxilin-eosin, periodic-acid Schiff staining (PAS) or van Gieson staining

Results

Biomicroscopy disclosed the presence of a Soemmerring's ring behind the iris in all cases. In one case (8) the lenticular remnants were clear and had a yellow colour while in all other cases the Soemmerring's ring was at least partially opacified and had a grayisch-white colour. The posterior capsule was intact in all but two cases (3 and 7) where a primary or a secondary capsulotomy had been performed respectively. Elschnig's pearls were visible on the posterior capsule of specimens 1 and 4. In all specimens except no. 7 folds were present in the posterior capsule.

Scanning electron microscopy (SEM)

In specimen 5 the ring had a maximum anterior-posterior capsule distance of approximately 1 mm while the maximum thickness in specimen 10 was 70 um. All others ranged in between and no relationship between inplantation time or lens type and thickness of the ring could be found.

A low power view of Soemmerring's ring with the zonular fibers and the ciliary processes is shown in Fig 1. The attachment of the zonular fibers to the ring deviated from the situation in an intact lens with regard to the equatorial compressed rim of the capsule (Fig. 1, arrow). The fibers themselves showed no fine structural alterations. Furthermore the SEM observations confirmed the biomicroscopic observation of the common presence of

folds in the posterior capsule.

The inside of Soemmerring's ring exhibited after fracturing almost normal lenticular fibers superficially (Fig. 2a), disturbed and degenerated fibers in deeper aspects of the ring (Fig. 2b) and amorphous parts in the center (see subsequent section). The subcapsular epithelium and the capsule itself revealed no abnormalities at the SEM level. In all specimens except 5 and 10 epithelial outgrowth was found covering both the anterior side of Soemmerring's ring and the corneal side of the posterior capsule encircled by this ring.

Light microscopy

Light microscopy disclosed a gradual change from normal fibers in the superficial parts to cataractous areas in the central region of the ring (Fig. 3a). No calcarious regions were found. The anterior side of the ring had a subcapsular epithelial lining whereas along the posterior capsule only randomly scattered groups of epithelial cells were found (Fig. 3b, asterisk). In the equatorial rim epithelial cells were found (Fig. 3b, arrow).

The wall of the ring consisted of capsular material, the anterior capsular flap being much thicker than its posterior counterpart, as in normal lenses. The fusion place of the anterior capsular flap with the posterior capsule sometimes showed loose appositioning (Fig. 3a), sometimes fibrinous material sealing the anterior to the posterior capsule (Fig. 4). In the three specimens examined light microscopically epithelial cells were present in this region of apposition and they were also found on the posterior capsule.

The organization of the fusion place was studied more carefully. At the free end of the anterior capsule the subcapsular epithelium in specimens 1 and 4 passed onto the anterior face of the anterior capsule forming a supracapsular monolayer of flattened epithelial cells. The free end of the anterior capsule in case 4 showed a swelling, predominantly filled with fibrillar material (Fig. 5). In specimen 9 a monolayer of cells transversed the fusion place, covering the posterior capsule.

The contents of the ring close to the fusion place consisted of epithelial cells, fibrillar material and also large cells, characterized by a foamy appearance due to numerous vacuoles and darkly-stained granules (Fig. 5, arrows).

Transmission electron microscopy (TEM)

The equatorial cells (Fig. 6) appeared as normal differentiating lens fibers. The nuclei were elongated with only small amounts of heterochromatin and one or two small nucleoli. The nuclear envelope was disappearing.

The cytoplasm contained few or no cellorganelles. Some lysosomal inclusion bodies were found (Fig. 7).

The epithelial cells were highly vacuolized and contained a cell nuclues with numerous patches of marginal heterochromatin (Fig. 8). Apart from vacuoles the cytoplasm contained free ribosomes, cisterns of rough endoplasmic reticulum and mitochondria which were partly swollen (Fig. 9). As in the lens fibres, epithelial cells contained lysosomes with multilamellar inclusions (see Fig. 7).

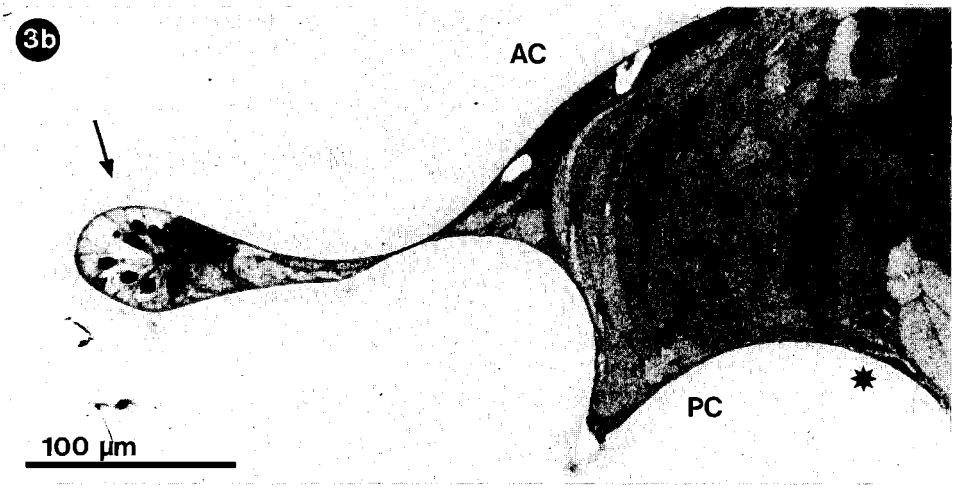
Between the subcapsular epithelium and the capsule a free space was found filled with fibrils, partly lying in groups (Fig. 9, arrows).

In the region of fusion between anterior and posterior capsule numerous leucocytes were found (Fig. 10). These were the large cells which were already noticed by light microscopy (see Fig. 5 , arrow). Their size varied from 10-20 um. These cells contained large, lobulated nuclei, cisterns of rough endoplasmic reticulum, lysosomes, glycogen granules, vesicles and vacuoles. The cell membrane had many folds and/or microvillous projections. In some of these cells numerous filaments were observed.

Discussion

Since the first description of the histology of lens remnants after ECCE in 1828 (Soemmerring, 1828) and some later publications concerning light microscopic investigations of this phenomenon (Wessely,1910, Poos, 1931, Stokoe, 1957, for review see Duke-Elder, 1969) remarkably little has been published on the lens remnants in pseudophakic eyes. It is generally suggested that the lenticular epithelium which may be entrapped in the periphery of the capsular bag is the dominant contributor to the development of after-cataract or posterior capsule opacification., The high incidence of posterior capsule opacification is a major disadvantage of ECCE (Champion, 1985). Hyperplasia of lens epithelium with wrinkling of the posterior capsule is more or less the rule and formation of Elschnig's pearls is found in a great number of cases (Champion, 1985). The Elschnig's pearls are differentiation products of lenticular epithelium as shown in previous papers (Kappelhof, 1986). The capsular wrinkling is thought to be caused by myofibroblastic differentiation of hyperplastic lens epithelium or fibroblasts of unknown origin on the anterior surface of the posterior capsule (Champion, 1985).

The results of this study agree with the results of an experimental study in rabbits (Kappelhof, 1985). Soemmerrings's rings in rabbits three weeks up to 12 months postoperatively disclosed the same gradual change from normal fibers superficially to cataractous regions in the center of the ring. The fact that cataractous regions were found in rabbits without preexistent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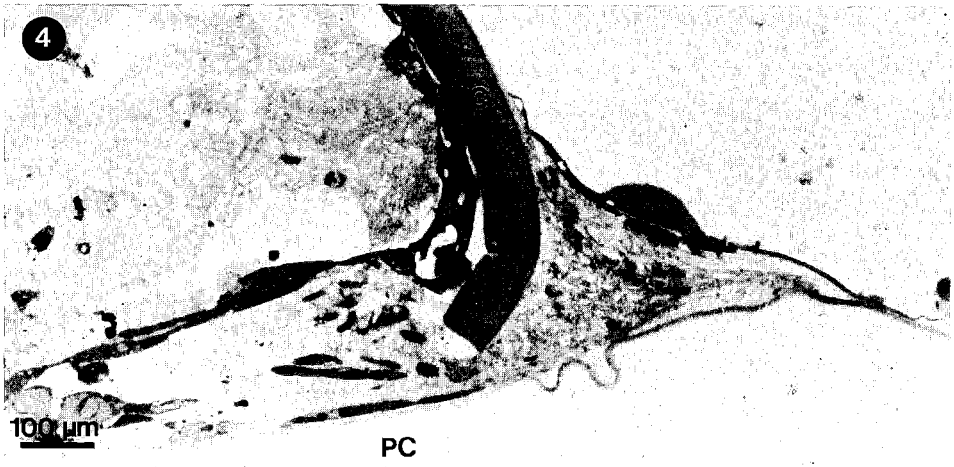
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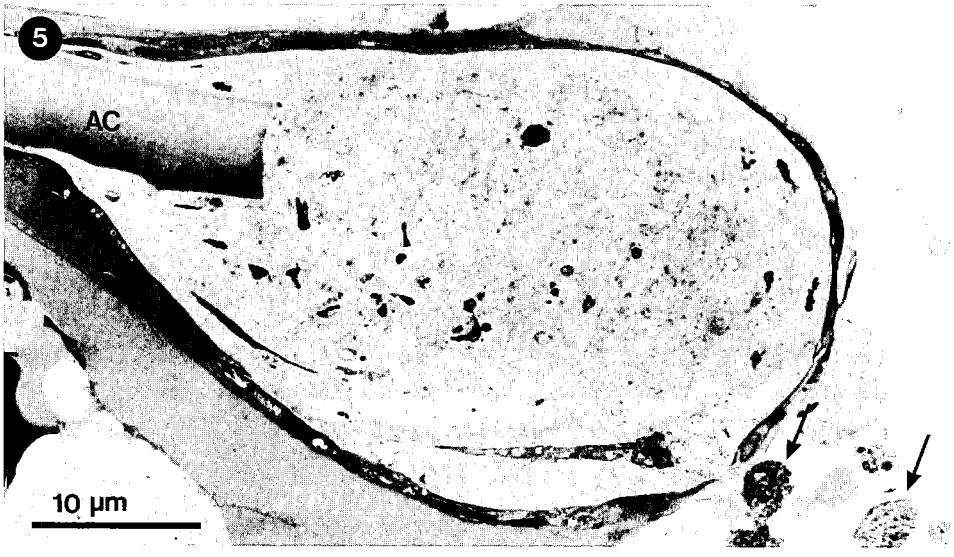
5
AC
10 µm

cataract made us assume that the cataractous regions in human material were also formed after the extracapsular cataract extraction. As is shown, lenticular epithelial cells, retained peripherally in the capsular bag, continue to divide and to differentiate into lenticular fibres. These fibers seem to get pushed towards the center of the ring where they degenerate and become cataractous. The epithelial cells on the posterior capsule and on the outside of Soemmerring's Rings were described before (Champion, 1985). They are proved to be of lenticular origin, as they are shown to be continous with the subcapsular epithelial cells. Epithelial cells were noticed in this study to traverse the fusion place of Soemmerring's Rings. The sealing of the anterior to the posterior capsule seems fibrinous in origin and it might well be that the different kinds of leukocytes found in the Soemmerrings's ring play a role in opening this sealing. The finding of leukocytes in the ring itself seems remarkable and was not noticed before. However, it is well-known that macrophages can be found in great numbers on an intraocular lens especially after a short implantation time (Guha, 1951, Wolter, 1982 and 1985).

Calcified regions, commonly found in congenital after-cataract, were not found in Soemmerring's ring. Probably it takes more time for cataractous regions to calcify.

A space between epithelial cells and lens capsule containing fibrillar material has been described before in posterior capsule opacification (McDonnell, 1983). In this study epithelial cells covering the corneal side of the anterior capsule demonstrated the same phenomenon. It seems likely that the secretion of fibrillar material by epithelial cells is a normal reaction of these cells. Subcapsular epithelial cells in the intact lens are supposed to do the same and this may be the cause of the thickening of the anterior lens capsule during lifetime. The lack of internal pressure as in an intact lens can be the reason for the loose accumulation of fibres.

Retained lenticular epithelium in the capsular bag after ECCE can hardly be avoided because the anterior capsule is lined with it and the equator contains actively dividing epithelium. This epithelium will not completely be destroyed using routine surgical techniques. Formation of a Soemmerrings's ring and epithelial outgrowth seems to be an unavoidable result of ECCE with the consequences for the occurrence of after-cataract, without drastic improvements of the irrigation of the equatorial region or suppression of the mitotic activity of the remaining epithelial cells.

Acknowledgements

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Table 1. Clinical data on the pseudophakic eyes used in this study

No.	Age (yrs)	Sex (M/F)	OD/OS	Type of IOL	Implant time (months)	SEM/ TEM/ LM
1	80	M	OS	Medallion	53	SEM,TEM,LM
2	77	F	OS	Iridocaps	4	SEM
3[a]	88	F	OD	Iridocaps	36	SEM
4	71	M	OS	Iridocaps	39	SEM,TEM,LM
5[b]	67	M	OS	Iridocaps	44	SEM
6[b]	67	M	OD	Iridocaps	48	SEM
7[a]	88	F	OS	Iridocaps	50	SEM
8	82	M	OD	Pearce	2	SEM
9	64	M	OD	Pearce	8	SEM,TEM,LM
10	67	F	OS	Pearce	9.5	SEM
11	82	F	OS	Pearce	17	SEM

[a] = same patient
[b] = same patient

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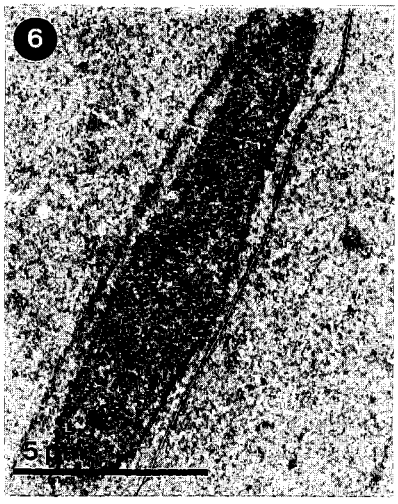
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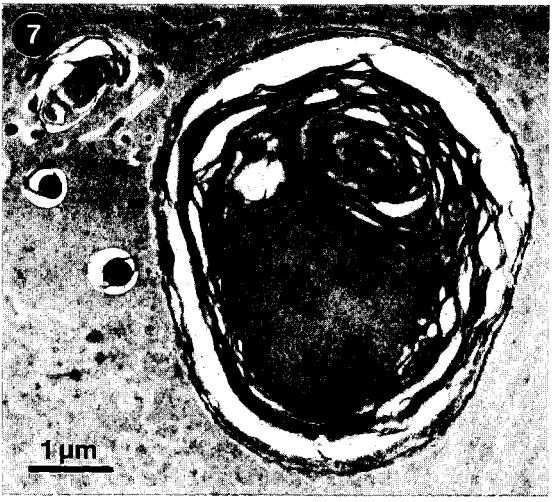
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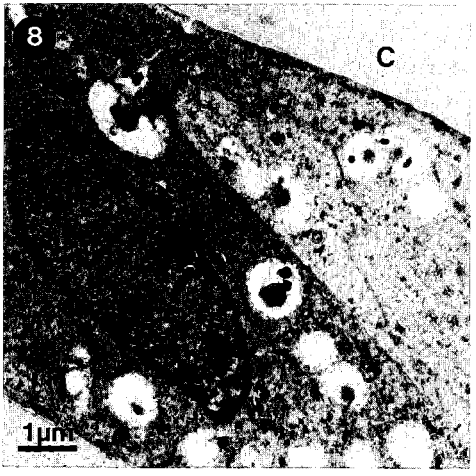
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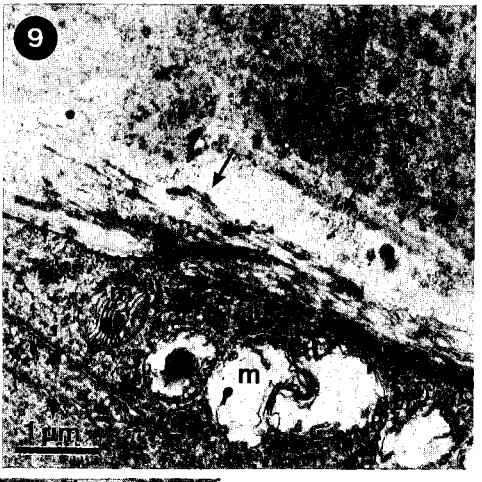
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Legends

Fig. 1 : Low power SEM view of the posterior side of the anterior segment (specimen 1, see Table I0), illustrating Soemmerring's ring with zonular fibres and ciliary processes. The posterior capsule (asterisk) has been torn during the preparation. The arrow indicates the compressed capsular rim at the equator (10x).

Fig. 2a : SEM picture illustrating normal superficial fibers in Soemmerring's ring (specimen 5, see Table I). The asterisk indicates the lens capsule (2100 x).

Fig. 2b : SEM picture of disturbed (arrow) and degenerated (asterisk) lenticular fibers in deeper aspects of Soemmerring's ring (specimen 2, see Table I, 350x).

Fig. 3a : LM of a transected Soemmerring's ring (specimen 4, see Table I). The central cataractous region is indicated by an asterisk. The anterior capsular flap is loosely appositioned to the posterior capsule (arrow) and Elschnig's pearls (arrowhead) are protruding into the pupillary space. AC: anterior capsule. PC: posterior capsule (toluidine blue staining, 36 x).

Fig. 3b : Detail of Fig. 3a. The equatorial part of Soemmerring's rings is compressed (arrow). In this area epithelial cells are present. The capsule is only faintly visible by the staining procedure. The asterisk indicates epithelial cells under the posterior capsule. AC: anterior capsule. PC: posterior capsule (toluidine blue staining, 360 x).

Fig. 4 : LM picture of the fusion place of the anterior capsular flap with the posterior capsule illustrating the fibrinous material between the anterior capsular flap and the posterior capsule (specimen 9, see Table I). AC: anterior capsule. PC: posterior capsule (toluidine blue staining, 125 x).

Fig. 5 : Detail of Fig. 3, arrow illustrating the swelling around the free end of the anterior capsular flap, covered with epithelium. Arrows indicate large, nucleated cells with a foamy appearance. AC: anterior capsule.

Fig. 6 : TEM picture of equatorial lenticular fibres in Soemmerring's ring (specimen 4, see Table I). The cytoplasm contains no cell organelles, the nucleus is elongated and lacks heterochromatin and the nuclear envelope is fading (6700 x).

Fig. 7 : Lysosomal inclusion bodies in lenticular fibers superficially in Soemmerring's ring (specimen 4, see Table I, 14.000 x).

Fig. 8 : TEM picture of epithelial cells, subcapsularly to the anterior capsule. Cells are highly vacuolized. C: capsule (specimen 4, see Table I, 10.000 x).

Fig. 9 : TEM picture illustrating the space between subcapsular epithelium and anterior lens capsule (C). This space contained many fibrils (arrows). In the epithelial cell swollen mitochondria are present (specimen 4, see Table I, 14.400 x).

Fig. 10 : TEM picture of a leucocyte in Soemmerring's ring (specimen 4, see Table I). Cells of this kind were found in the region of fusion between anterior and posterior capsule (cf. Fig. 5, arrows). This cell exhibits a multilobulated nucleus, microvillous projections of the cell membrane and numerous clear vesicles and dark vacuoles in the cytoplasm (6705 x).

4.2. An ultrastructural study of Elschnig's pearls in the pseudophakic eye (American Journal of Ophthalmology 101: 58-69, 1986).

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Summary

In two pseudophakic human eyes, obtained post mortem, Elschnig's pearls were visible biomicroscopically. One eye contained a medallion lens and the other an iridocapsular lens (implanted for 53 months and 39 months, respectively). The medallion lens was fixed to the iris but was not attached to the Soemmerring's ring. Elschnig's pearls and star-shaped cells were found on the posterior capsule in the pupillary space. One loop of the iridocapsular lens was encased in the Soemmerring's ring whereas the other was located between the iris and the lens remnants. The Elschnig's pearls were on the anterior side of the ring; only a few were in the pupillary space.

Two other pseudophakic eyes with clear posterior capsules also contained small numbers of Elschnig's pearls on or just near the peripheral lens remnants.

Introduction

Extracapsular cataract extraction can produce a great variety of complications[1]. One of the more common long-term complications is the opacification of the posterior capsule. In adults, the incidence is approximately 50% after three to five years [2] and children and young adults seem to be even more susceptible to this complication[3]. Opacification of the posterior capsule is also termed secondary membrane or after-cataract. [4]

After-cataract may cause visual obstruction and is therefore a clinically

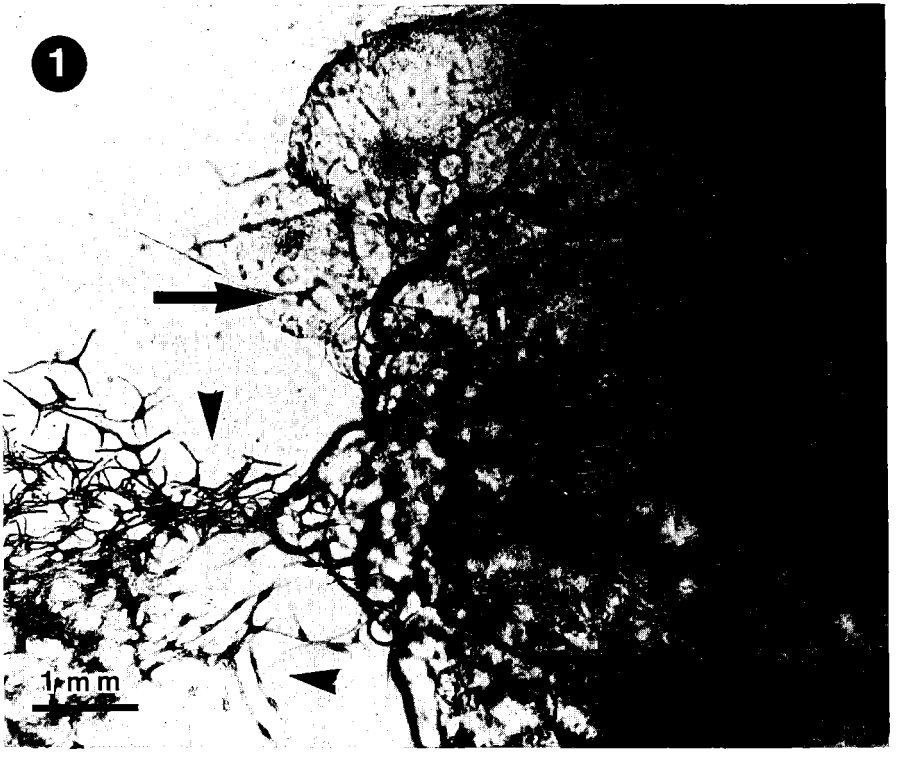
important phenomenon. The formation of after-cataract is ofter associated with Elschnig's pearls, also termed globular or bladder cells.[4] Few studies have been devoted to these transparent, globular structures, which vary in size and frequency. Visual acuity may be affected by the pearls, depending on their protrusions into the pupillary space. Morphologic investigations disclose that they protrude from the space between the intact posterior capsule and the anterior capsular flap which is left behind after extracapsular cataract extraction.[5]

Elschnig's pearls appear to stain homogenously with hematoxylin and Congo red and some are nucleated.[5] Each pearl represents one cell; hence, they are also referred to as giant cells.[6] Elschnig's pearls are regarded as representing aberrant attempts of the lenticular epithelium to form new fibers.[4] The globular shape of the structure is thought to result from the absence of the normal internal lenticular pressure so that the growing epithelial cells develop into an abnormal spherical shape.[7] We studied the overall morphologic, light microscopic and ultrastructural features of Elschnig's pearls in pseudophakic human eyes obtained post mortem. We paid special attention to the possible role of the loop of the intraocular lens in the formation of Elschnig's pearls.

Table
Summary of clinical data

eye	type of IOL	length of implantation (mos)	age of patient (yrs)	clinical symptoms
A	1	53	80	Elschnig's pearls
B	2	39	72	Elschnig's pearls
C	2	48	67	clear post.capsule
D	2	44	87	clear post.capsule

1= Medallion lens (transiridectomy-fixated)
2= Binkhorst four-loop (iris-clip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Material and Methods

In this study, two human pseudophakic eyes, obtained post mortem and containing Elschnig's pearls, were investigated by biomicroscopy, light microscopy, scanning electron microscopy, and transmission electron microscopy. We also examined two pseudophakic eyes containing no biomicroscopically visible Elschnig's pearls and with clear posterior capsule by biomicroscopy and scanning electron microscopy. The Table summarizes the clinical data for these four eyes.

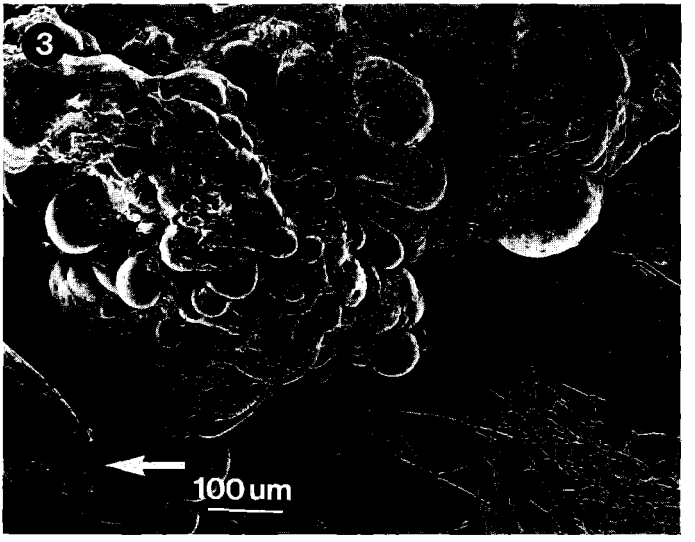
After enucleation the eyes were inspected biomicroscopically and fixed in a cacodylate buffered mixture of paraformaldehyde 1% and glutaraldehyde 1.25% (pH, 7.4; total osmolarity, 530 mOsm).[8] Fixation time varied between five and ten days. The cornea and the posterior halves of the globes were dissected after fixation. The anterior segments of eyes A, C and D and a part of the anterior segment of eye B were processed for scanning electron microscopy by dehydration in an ascendibng series of ethanols and critical point dried with carbon dioxide. The dried specimens were glued in toto to aluminium specimen mount with conductive carbon cement, gold-coated, and viewed in a scanning electron microscope.

After removal from the mount, the specimens were fractured. Some pieces were gold-coated for inspection of the fracture planes by scanning electron microscopy while other pieces were postfixed in osmium tetroxide 1% and embedded in Epon 812. For light microscopy, we stained semithin sections (1 um) of this osmificated material with toluidine blue. Ultrathin sections were stained with uranyl acetate and lead citrate and examined in a transmission electron microscope.

The anterior segment of eye B was used partly for scanning electron microscopy and partly for transmission electron microscopy, using the procedures described for the other specimens.

Results

Biomicroscopic examination of eyes A and B disclosed wrinkled posterior capsules with groups of transparent globular structures extending from the periphery into the pupillary space. In eye A many star-shaped cells were present in the center of the posterior capsule (Fig 1). After the dissection procedures, the posterior view of the anterior segment showed ring-shaped peripheral lens remnants (a Soemmerring's ring). The Elschnig's pearls in both specimens seemed to originate in this ring structure. Some of the ciliary processes in eye A (medallion lens) showed distortion and elongation. This intraocular lens was not encapsulated in peripheral lens material. One of the loops of the iridocapsular lens in eye B was encased in the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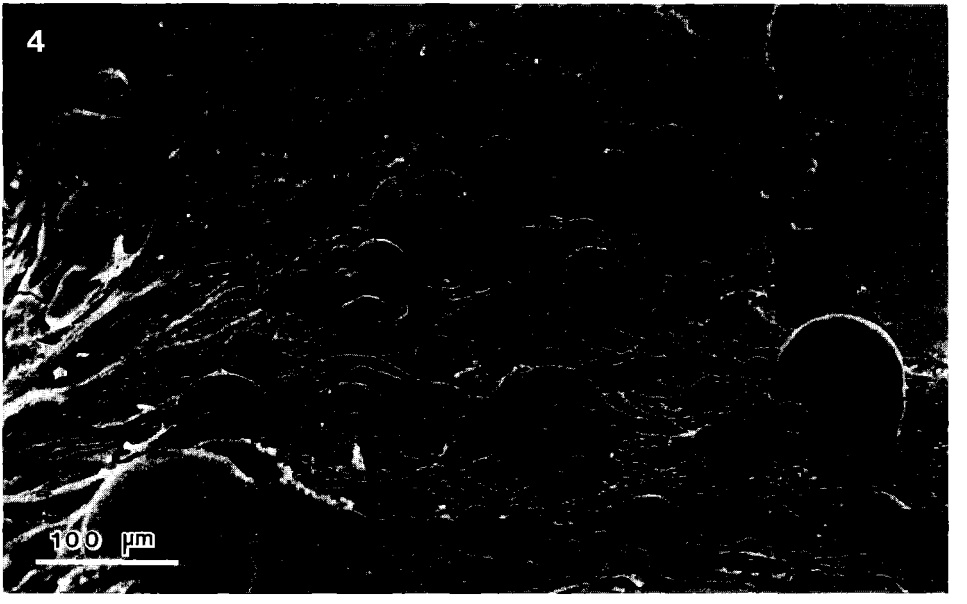
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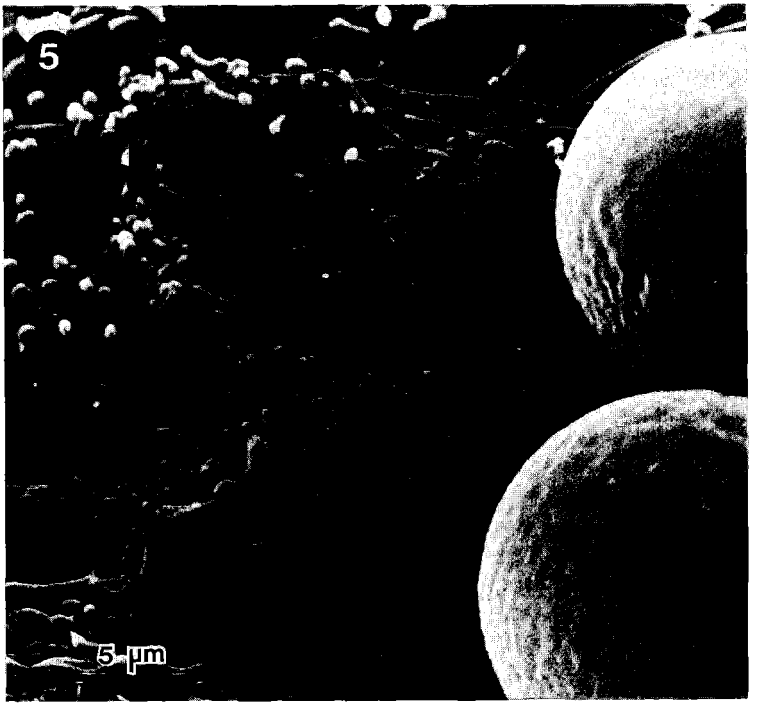
Soemmerring's ring whereas the other was located between the iris and the lens remnants without adhesions. Our ultrastructural observations were focussed on the Elschnig's pearls and their relationship with the lens remnants and the intraocular lens.

Scanning electron microscopy confirmed the biomicroscopic observations. In eye A the medallion lens proved to be free of the Soemmerring's ring but was fixed to the iris (Fig 2). After removal of the intraocular lens the Elschnig's pearls and the star-shaped cells were found on the posterior capsule in the pupillary space (Fig 3). In eye B many of the Elschnig's pearls were on the anterior side of the Soemmerring's ring and only a few protruded into the pupillary space. The Elschnig's pearls appeared as globular structures, piled up and ranging in diameter from 5 to 120 um. At higher magnification the elongated form of the basal part of the Elschnig's pearls was clearly visible (Fig 4).

In both specimens the surface structure of the Elschnig's pearls varied. Some of the membranes were almost smooth whereas others were covered with microvilli (Fig 5). The star-shaped cells on the anterior side of the posterior capsule of eye A were uniform in size. They were located in the center and their protrusions approached the Elschnig's pearls. In some parts their processes were in close contact with each other and formed a cellular network. The surface structure of these cells was not smooth but did not have the filamentous aspect found in the Elschnig's pearls (Fig 6). The Elschnig's pearls bulged from the gap between the intact posterior capsule and the anterior capsular flap. These capsular remains enclosed the equatorial part of the lens, left behind after extracapsular cataract extraction. Inspection of the fractured Soemmerring's ring in eye A showed that these capsules had failed to adhere in some places or had opened again (Fig 7). In eye B one of the loops of the intraocular lens seperated the anterior and posterior capsule, leaving a space where cellular elements bulged out (Fig 8).

Light microscopy showed the inner structure of the Elschnig's pearls. Their cytoplasm stained homogenously with toluidine blue and some showed a nucleus. Serial sections of eye A showed that almost all the pearls were nucleated with the nucleus sometimes located within the basal, slender part of the cell. The nuclei were sometimes round or oval but more often they appeared to be lobulated. In some sections this indentation gave the impression that the pearls were multinucleated (Fig 9). We carefully examined the area at which the anterior capsular flap approached the posterior capsule and observed that the two were not closely appositioned (Fig 10). At this point cellular material could be found between the two capsules. These cellular elements were indistinguishable from Elschnig's pearls. The anterior capsular flap was subcapsularly lined with a single layer of epithelium. This epithelium also covered the outside of the Soemmerring's ring (Fig 11).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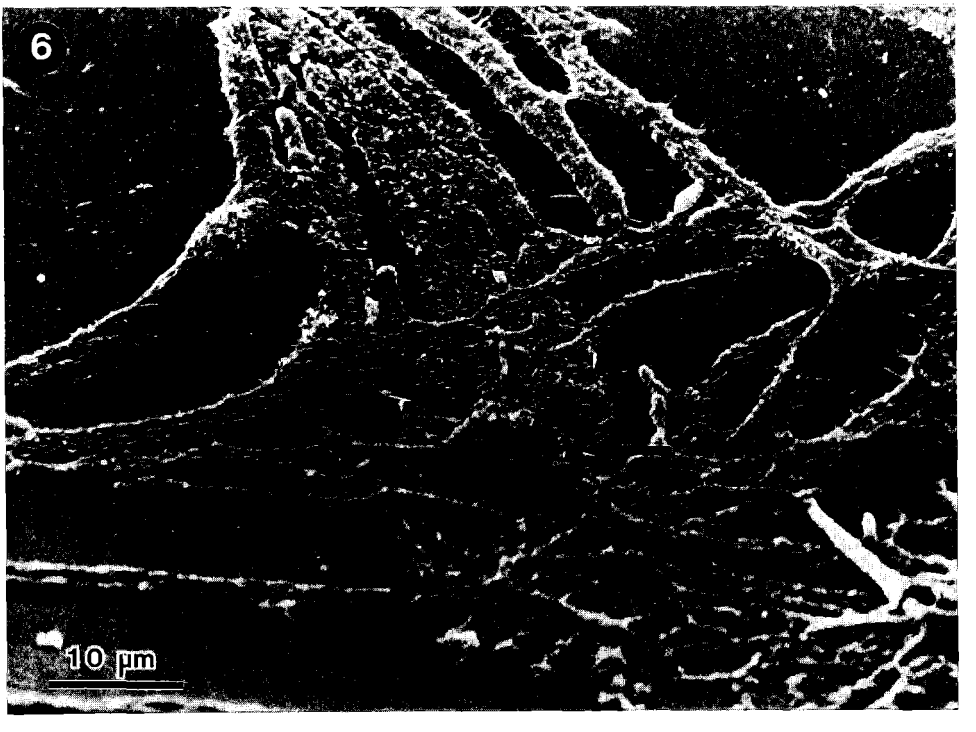
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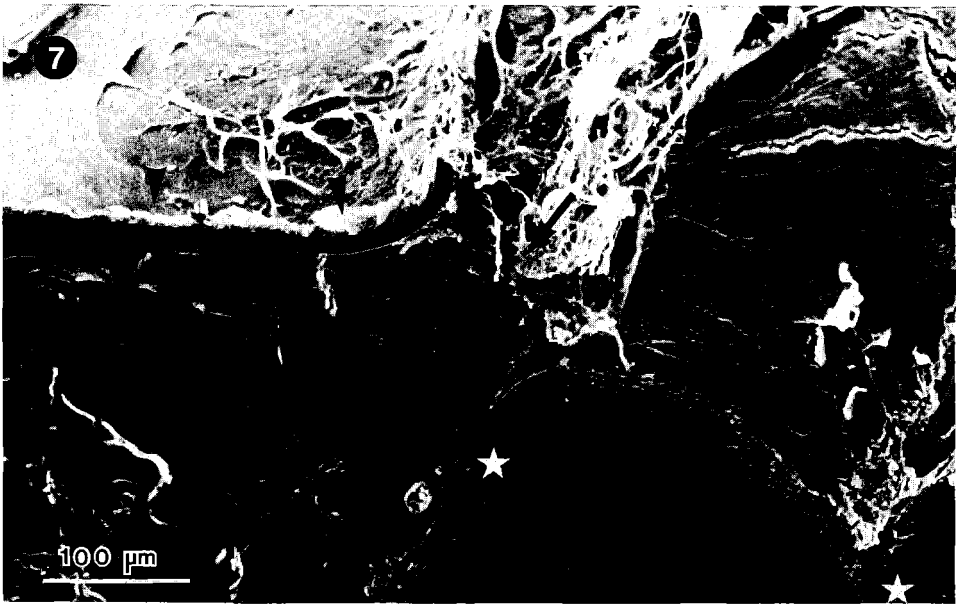
Transmission electron microscopy disclosed a homogenous cytoplasm with a fine granular aspect and almost no cell organelles. A rare vesicular body or vacuole could be found apart from the nucleus. The nuclei contained one or two nucleoli free of associated chromatin. The complex indentations of the nuclear envelope were obvious. In many places membranes of adjacent Elschnig's pearls showed interdigitations with gap junctions and structures resembling desmosomes (Fig 12). The mebranes of the most superficial Elschnig's pearls exhibited the microvillous surface observed on scanning electron microscopy (Fig 13). The posterior lens capsule had an amorphous structure with a thickness of about 5 um. There was a space between the posterior capsule and the Elschnig's pearls measuring 0.5 to 2 um wide. This space was electron-lucent and the capsule near this space demonstrated fibrillar elements (Fig 14).

Eyes C and D had smooth posterior capsules without adhering cellular material. In eye C both loops of the intraocular lens were encased between the anterior capsular flap and the intact posterior capsule. In eye D one loop was in the same position whereas the other was free of adhesions. In neither specimen was a gap between the anterior capsular flap and the posterior capsule apparent. As in the fractured specimen, both capsules had adhered tightly (Fig 15). More careful examination, however, enclosed globular elements in both eyes C and D. In eye C the Elschnig's pearls were hidden behind the iris and were detected only after dissection. They protruded from the site of fusion of the two capsules just near the place where one of the loops was enmeshed (Fig 16). In eye D few globular elements were detected by scanning electron microscopy. They were located in groups on the anterior side of the Soemmerring's ring where there appeared to be breaks in the capsule (Fig 17).

Discussion

In 1901 Hirschberg[9] was the first to describe in humans what came to be called Elschnig's pearls. In 1911 Elschnig[5] provided a detailed description of his light microscopic investigations concerning this phenomenon in after-cataract formation. Elschnig's pearls were described as semiglobular and globular structures piled on the posterior capsule.[5,9] Elschnig's pearls were thought to be caused by the opening in the capsule. Originating from the space between the posterior capsule and the anterior capsular flap, Elschnig's pearls extended into the pupillary space. Elschnig himself regarded them as lens epithelium which had escaped from the Soemmerring's ring and grown into aberrant fibers because of the lack of normal internal pressure from the intact lens. Since then only a few morphologic studies concerning Elschnig's pearls have been published.[10-14] Recent arti-


7
100 µm


8
250 µm

cles concerning after-cataractous changes, however, have dealt with the ultrastructure of epithelial cells found on the posterior capsule after extracapsular cataract extarction. [10,12,15-18]

In animal models (cats and rabbits) it has been demonstrated that the anterior lens epithelium proliferated on the posterior capsule, forming multiple layers.[10,12,17] In cats Elschnig's pearls are rounded or oval, perfectly transparent structures occasionaly covered with anterior capsule.[10] In rabbits Elschnig's pearls are uncommon, although posterior capsule opacification after extracapsular cataract extraction is prominent. [12,17-19]

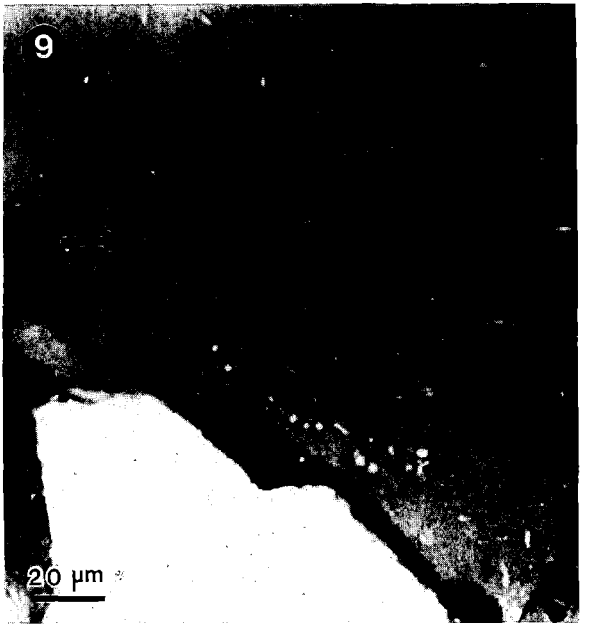
In humans, epithelial cells of the anterior lens capsule together with iris stromal cells form opaque membranes.[12] The intraocular lens is thought to act as a scaffold for proliferating cells.[12] McDonnell, Zarbin and Green[16] found that the fibrous membranes in posterior capsule opacification consisted of hyperplastic lens epithelium that had apparently undergone fibrous metaplasia. These cellular aggregates always originated at the site of apposition between the anterior capsular flap and the posterior capsule. They considered the epithelial nature of the cellular material to be proven by the formation of a basement membrane and the presence of interdigitating cytoplasmic processes and desmosomes.

In our study, Elschnig's pearls exhibited some characteristics of epithelial cells (for example, interdigitating processes and structures resembling desmosomes between adjacent cells and microvilli on the free surface). We could not demonstrate the formation of a basement membrane by Elschnig's pearls. The fine granular cytoplasm, the gap junctions, and the lack of cell organelles on transmission electron microscopy suggested that Elschnig's pearls are lens epithelial cells differentiating into lenticular fibers. This confirmed previous suggestions.[9-11] All Elschnig's pearls in eye A may have possessed a nucleus because of unfinished differentiation or because of abnormal differentiation. Eyes B, C and D did not undergo serial sectioning.

Although Elschnig's pearls have been described as globular, our study showed they can exhibit long and slender shapes on scanning electron microscpy and, therefore, that the spherical form is only one variety of the cell (Fig 4). The gap between the posterior and anterior capsule of the Soemmerring's ring is thought to be a primary causative factor.[5,11,12]

The intraocular lens loops in a pseudophakic eye can act as a mechanical element to initiate separation of the capsules, as Hiles and Johnson[12] suggested. Although our results seem to be in accordance with this idea, further substantiation is needed before broad conclusions can be drawn.

The origin of the star-shaped cells found centrally on the posterior capsule of eye A remains unclear. Their shape shows some resmblance to the pigmented star cells which are a frequent congenital anomaly.[20] Because of their fibroblast-like appearance on scanning electron microscopy, it seems likely that they were derived from the iris stroma.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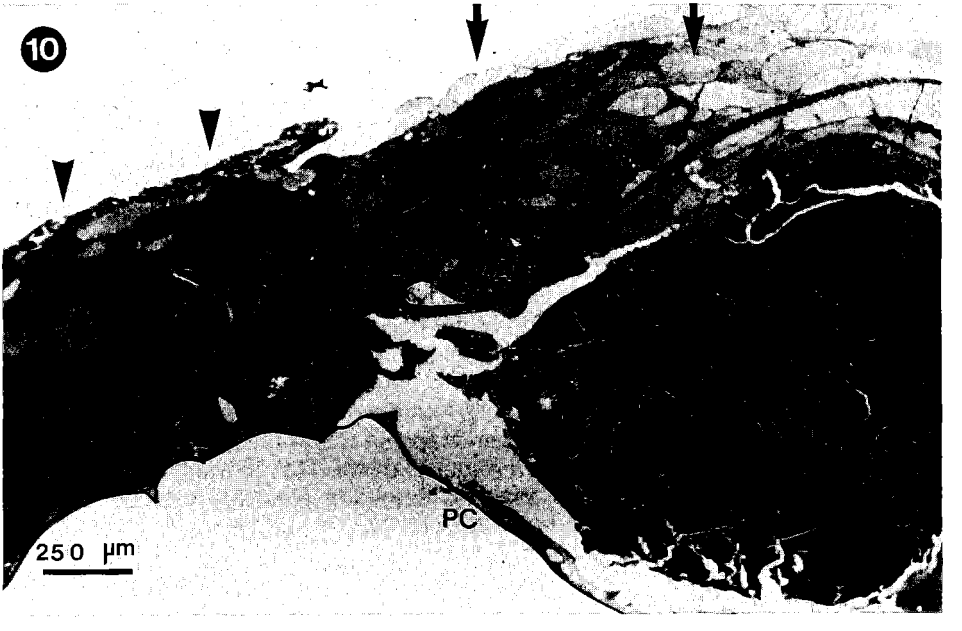
10
PC
250 µm

Study of eyes C and D, in which no obvious Elschnig's pearls were found after biomicroscopic inspection, disclosed a small number of globular elements (Elschnig's pearls) either at the junction of the anterior and posterior capsule or at breaks in the anterior part of Soemmerring's ring. In the latter case we observed that although the anterior and posterior capsule adhered tightly all along the inner side of Soemmerring's ring, there were breaks on the anterior side of the capsule. Epithelial cells grow through these breaks; this was also found by Hiles and Johnson[12] in the rabbit.

Proliferation of epithelial cells outside the ring of Soemmerring is much more frequent than biomicroscopic examination suggests. However, this phenomenon is only clinically relevant if the proliferating epithelial cells extend into the pupillary space. A complete suppression of this phenomenon might be obtained if all epithelial cells located in the lens bow region were removed during extracapsular cataract extraction but it is doubtful whether this will ever be achieved.

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11
20 µm


12
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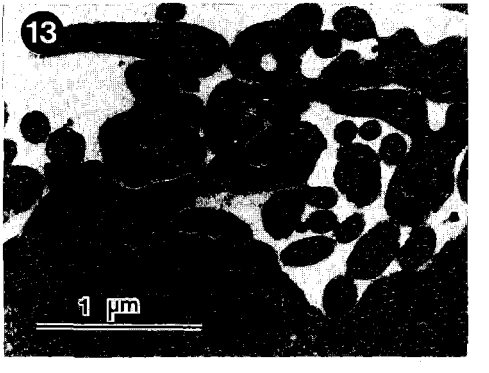
13
1 µm

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14
0.5 µm


15
250 µm

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Legends

Fig 1. In eye A, Elschnig's pearls extend from the pupillary margin into the pupillary space (arrow). More centrally, star-shaped cells can be seen (arrowheads) (x20).

Fig 2. Anterior aspect of eye A with the medallion intraocular lens in situ. The cornea is dissected. I, iris; S, sclera (x16)

Fig 3. Elschnig's pearls in eye A extend from the pupillary margin into the pupillary space (same area shown in Figure 1). The star-shaped cells are also visible (arrowhead). The partially visible cut loop of the intraocular lens is indicated by an arrow (x125).

Fig 4. Elschnig's pearls on the posterior capsule (PC) of eye A. The long and slender shape of the base of some of the pearls is indicated by arrows (x250).

Fig 5. Surface of the Elschnig's pearls in eye B. Two smaller, smooth-surfaced pearls can be seen on the microvillous surface of a bigger one (arrows) (x3,800)

Fig 6. Star-shaped cells on the posterior capsule in eye A. Nuclei are indicated by arrows (x2,000).

Fig 7. Fractured Soemmerring's ring in eye A, showing the place of adherence between the anterior capsular flap and the posterior capsule on transection. A gap between the capsules permits cellular material to escape from the ring (arrows). Arrowheads, anterior capsule; stars, posterior capsule (x 270)

Fig 8. Intraocular lens loop (arrowheads) enmeshed in the Soemmerring's ring in eye B. The capsules are seperated, leaving a gap, in which globular


16
AC
PC
100 µm


17
5 µm

elements protrude (arrows). The posterior capsule, indicated by a star, is torn as a result of the preparation (x75).

Fig 9. Elschnig's pearls on the posterior capsule in eye A. The lobulated nuclei (with nucleoli) are clearly visible (arrows). The membranes are partly stained heterogenously (toluidine blue, x600).

Fig 10. Soemmerring's ring in eye A with Elschnig's pearls on the posterior capsule (arrowheads) and on top of the Soemmerring's ring (arrows). The center of Soemmerring's ring has an amorphous structure (star); the gap between the anterior capsule (AC) and the posterior capsule (PC) is filled by cellular elements (toluidine blue, x60)

Fig 11. Eye a. The anterior capsular flap with the subcapsular epithelial lining (arrows) growing over the curled up margin onto the outside of the anterior capsule. Elschnig's pearls are lying on top of the anterior capsule (toluidine blue, x1,000).

Fig 12. Eye B. Interdigitations in the mebranes of adjacent Elschnig's pearls. The arrow indicates a gap junction. Arrowheads, structures resembling desmosomes (x6,000).

Fig 13. The microvilli on the free surface of the Elschnig's pearls in eye B (x3,000).

Fig 14. Eye B. The electron-lucent space between the posterior capsule and the Elschnig's pearls (ep). Fibrillar elements are indicated by arrowheads. C, capsule (x5,000).

Fig 15. Section of Soemmerring's ring in eye C. The area of fusion between the anterior capsule and the posterior capsule is indicated by the arrow (x84).

Fig 16. Elschnig's pearls in eye C, situated on the Soemmerring's ring just near the place where one of the loops of the intraocular lens (arrow) was enmeshed. The Elschnig's pearls are indicated by arrowheads. PC, posterior capsule; AC, anterior capsule (x110).

Fig 17. Elschnig's pearls in eye D, situated on the Soemmerring's ring in small numbers. Breaks in the capsule seemed to be present in these locations (x2,800).

4.3. Cytology of human intraocular lenses. A scanning electron microscopic study (Ophthalmic Research 18: 75-80, 1986).

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Introduction

Inspection of intraocular lenses (IOLs), removed from human eyes for varying reasons, reveals the presence of different types of adherent cells and other structures apparently of biological origin. For the study of these structures on the surface of the IOL, *Wolter* [1982a, b] developed the lens implant cytology technique. In this study we used a different technique, viz. scanning electron microscopy which has some advantages over the lens implant cytology technique but also some disadvantages. Advantageous are the clear 3-dimensional view and the higher resolution. However, scanning electron microscopy presupposes rather costly laboratory equipment and careful preparation and even then some artifacts remain. This report concerns the scanning electron microscopic study of 9 IOLs removed from human eyes after surgery. The results are discussed and related to literature.

Materials and Methods

During the past year various types of IOLs, removed for varying reasons, were sent to the Department of Morphology of the Netherlands Ophthalmic Research Institute.

Table I summarizes the type of IOL used, the implantation time and the reason for removal of each of the specimens studied. Obviously, most of the lenses were removed because of corneal complications. Of the 2 posterior chamber lenses, 1 was removed for inflammatory reasons and the other, a modified tripod lens with anterior loops on the optic, because of an intermittent touch. The implantation time varied between 5 months and 12 years. Each specimen was fixed in a cacodylate-buffered mixture of glutaraldehyde and paraformaldehyde [*Peters*, 1970] for several days with a maximum of 10 days. Consequently the specimens were dehydrated in a graded series of ethanols and critical point dried with CO_2. After gold coating the lenses were glued on a specimen mount using conductive carbon cement and inspected in a Philips SEM 505 scanning electron microscope.

In order to study the effect of scanning electron microscopic processing on the lenses, 10 new lenses with polymethylmethacrylate optics underwent various separate steps of these preparations. Different types of lenses, produced by different manufacturers, were used. Two lenses were studied after immersion in Peter's fixative for 3 days, 2 lenses after ethanol dehydration, 2 lenses after critical point drying with CO_2, 2 lenses after gold coating and finally 2 new lenses were studied after the whole preparation.

Table I

Lens No.	Type of IOL	Implantation time	Reason for removal
1	Rigid tripod	5 months	inflammation
2	Binkhorst-2	approx. 7 years	?
3	Binkhorst-2	approx. 3 years	keratopathy
4	Medallion lens	12 years	keratopathy
5	Binkhorst-2	3 years (37 months)	keratopathy
6	Binkhorst-2	7 years (83 months)	keratopathy
7	Medallion lens	approx. 2 years	keratopathy
8	Binkhorst-4	5 years	trauma
9	Modified tripod	13 months	intermittent touch

Discussion

The presence of macrophages and/or epitheloid cells and/or granulocytes on the surface of the implants 1–3 (table I) was not related to the presence of a clinically evident inflammatory reaction of the eye. This is in correspondence with the findings of *Sievers and von Domarus* [1984].

Lenses 4 and 5 (table I), on which endothelial cells were found, were both removed because of corneal complications. On 1 of the IOLs, not more than remnants of the adhering cells could be observed and, in this case (lens 3), it was hardly possible to determine the nature of the cellular material (fig. 7). Also fibroblasts or fibroblast-like cells could have been responsible for these remains, because fingerprints of cell processes could be seen on the surface of the IOL (fig. 6). The membrane fragments are supposed to be parts of the capsule which was described by *Wolter* [1982a, b] and by *Sievers and von Domarus* [1984]. *Wolter* [1982a, b] speculated that this membrane may sequester the IOL in the course of a foreign body reaction. The reason why only fragments could be found might be the destruction of this capsule during surgery or during preparation for scanning electron microscopy.

The lens with an almost clear surface (lens 9; table I) had been kept in saline for several hours after explantation before fixing it. This circumstance makes the finding of the clear surface unreliable because biological material could have been washed away. For this reason immediate fixation of the IOL is necessary.

The deformation and cracking of the polymethylmethacrylate optics of the implants have already been described by *Sievers and von Domarus* [1984]. The finding that these changes were caused by pressure is remarkable. Critical point drying is an inevitable step in the preparation for scanning electron microscopy, being designed to avoid surface tension during the drying process, which would disrupt the cells.

The degenerative changes in the polypropylene or nylon loops have been described many times before and they were found mostly in the bent parts of the loops [*Drews* et al., 1978; *Apple* et al., 1984].


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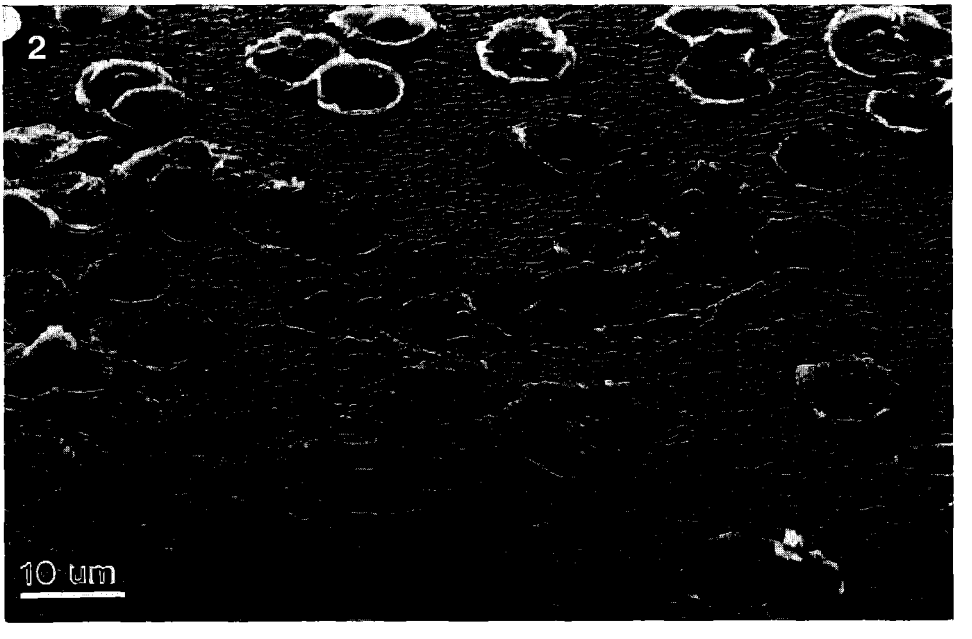
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Acknowledgements

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Fig. 1. High power scan of cells on the surface of a Binkhorst-2 IOL after 3 years of implantation. According to *Sievers and von Domarus* [1982], the cell with the fine processes is a macrophage or an epitheloid cell. The others can be lymphocytes or other types of granulocytes.

Fig. 2. High power scan of cells on the surface of a Worst medallion lens after 12 years of implantation. The implant was removed because of intermittent touch and these cells are supposed to be corneal endothelial cells.

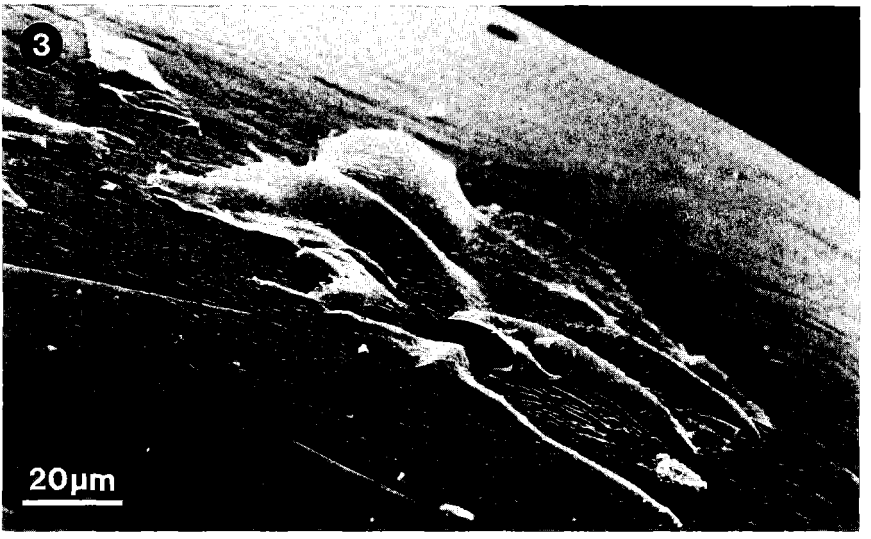
Fig. 3. High power scan of membrane fragments on the surface of a Binkhorst-2 IOL after 7 years of implantation. These fragments are regarded as the remnants of the fibroblastic response of the host versus the implant [*Wolter*, 1982a, b].

Fig. 4. High power scan of a blood clot around the optic of a Binkhorst-4 IOL which was removed after 5 years of implantation because of a severe trauma. Erythrocytes and fibrin threads are clearly visible, demonstrating the good quality of the imaging of cellular material in scanning electron microscopy.

Fig. 5. Low power scan of a Binkhorst-2 IOL after 37 months of implantation after its preparation for scanning electron microscopy. One of the optics was cut during explantation, the other was separately studied. Deformation of the optic and the cracking of its surface, due to the critical point drying, is clearly visible.

Fig. 6. Cracks and fissures in the optic of a Binkhorst-2 IOL after 83 months of implantation. These changes are not regarded as artificial but as the results of a biodegenerative process.

Fig. 7. Remains of cells, adherent to the anterior surface of a Binkhorst-2 IOL after 3 years of implantation. They are regarded as remains of corneal endothelial cells or remains of fibroblasts. Proper determination is impossible. This picture is from the same IOL as figure 1, so it seems unlikely that the preparation for SEM has anything to do with the cell ruptures.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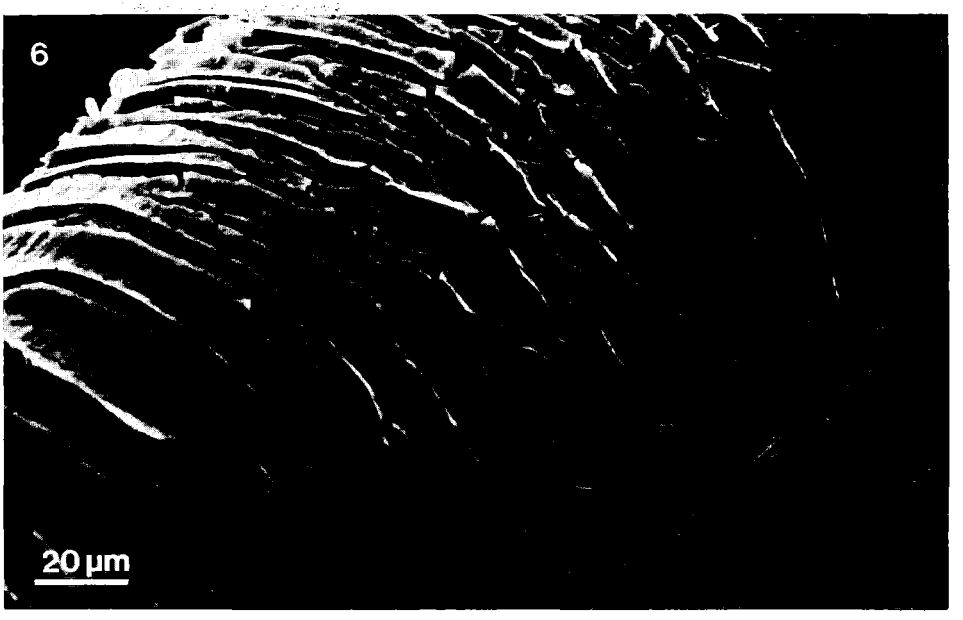
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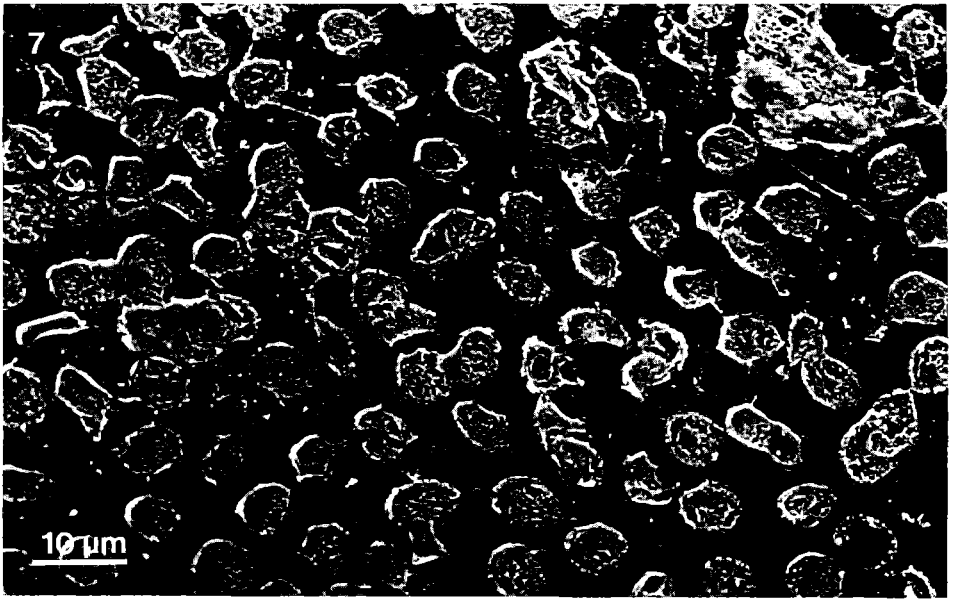
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4.4. Scanning electron microscopy of a 12-year old medallion lens (Implant 4: 10-16, 1986)

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Introduction

Since the introduction in 1949 of intraocular lenses (IOL) there has been a rapid development in lens styles and surgical procedures (1). Due to improvements patients are expected to tolerate intraocular lenses for a long period. In this light it becomes important to study the long term effect of implantation on the ocular tissues (2). Up till now, most studies were devoted to IOL's which had been implanted for short periods and only incidentally the effect of implantation periods of more than a few years were reported (3). The present report describes the fine structure of one of the first Worst medallion lenses ever implanted after a 12 years period in situ in the eye of a young male patient.

Case report

In 1972 a 12-year old boy was examined because because of an accidentally damaged right eye due to a nail that had penetrated his eye. The nail had perforated the cornea in the lower nasal quadrant and a traumatic cataract had developed. The patient was treated by extracapsular cataract extraction and implantation of a Worst medallion lens by the designer himself. This type of lens was still in an experimental stage adapted from a Binkhorst iridocapsular lens. The lens body was made of polymethylmethacrylate (PMMA) and the loops were made of supramid (polyamide). Postoperative vision was 0.8 for the injured right eye and 1.0 for the left eye.


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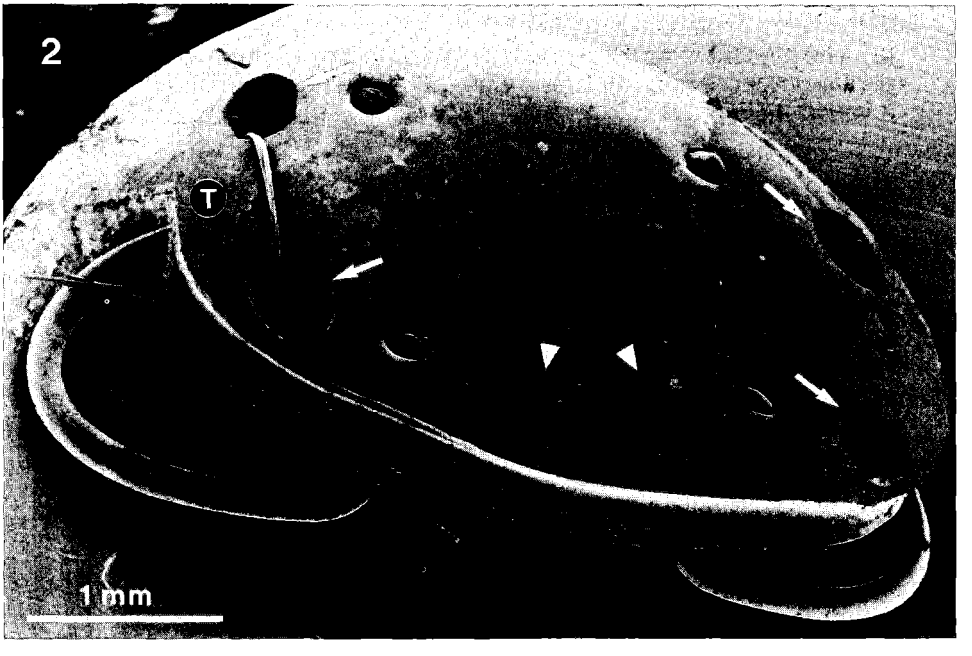
2
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Early 1984 the patient reattended the hospital because of decreased vision and pain in the right eye. The IOL appeared to be loosened from its iris-fixation suture at the temporal side. The sutures were made of perlon (polyamide). The lens was surgically refixed by use of a Strampelli metal thread. In july 1984 the young man attended the Department of Ophthalmology of the Free University in Amsterdam complaining of decreased vision. The vision was 0.4 for the right eye and the IOL was touching the cornea at the lower nasal quadrant (figure 1). A progressive corneal opacification in the lower nasal part with decreasing vision was a clinical indication for removal of the implant. There were no complications during surgery; the Strampelli thread was cut superiorly and removed. After this the IOL proved to be free of any adhesion. Postoperatively a progressive corneal clouding occured, which will force further therapy.

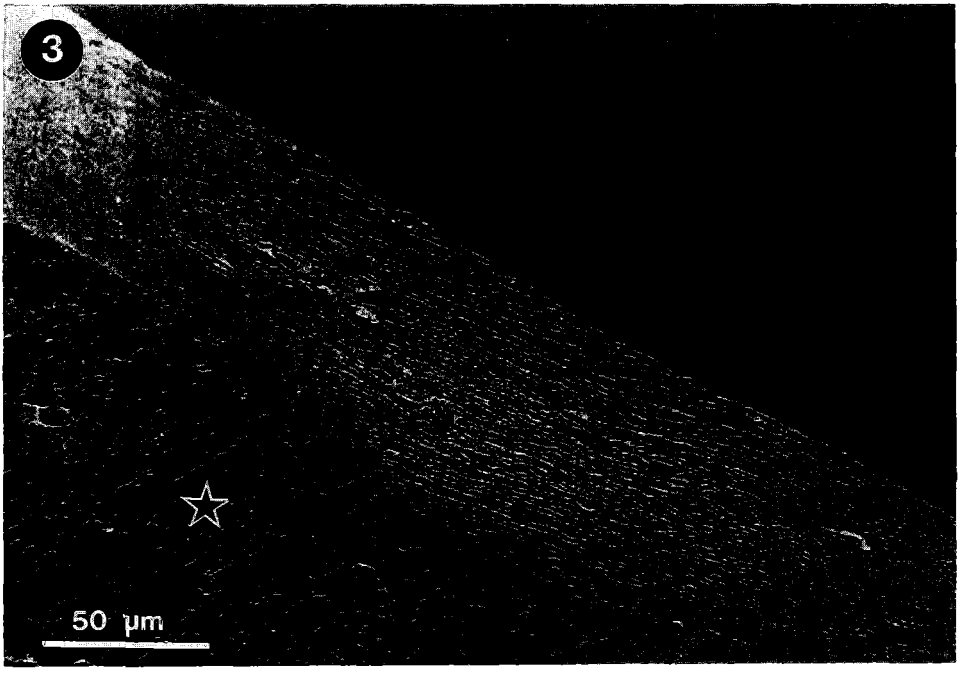
Materials and methods

The intraocular lens was fixed in a cacodylate buffered mixture of glutaraldehyde and paraformaldehyde according to Peters (4). After fixation the lens was rinsed in buffer, dehydrated in a graded series of ethanol up to 100% and subsequently critical point dried with carbon dioxide. During the whole processing for scanning electron microscopy the IOL was carefully handled because of the risk of washing away adherent materials. The specimen was glued on a mounting table with conductive carbon cement exposing its anterior surface, and after gold-coating it was studied in a Philips SEM 505 scanning electron microscope (figure 2). After inspecting and photographing the anterior side, the IOL was removed from the specimen mount, turned around and remounted, thus exposing the posterior side.

Results

1. The lens body

Remarkable features of both the posterior and anterior side of the IOL are the rough surface and the sharp edges (figure 3). Comparison with a recent IOL (figure 4) of different style emphasized this roughness. At high magnification this rough surface proved to be due to numerous grooves running randomly in all directions.
Adherent to both anterior and posterior surfaces were remnants of an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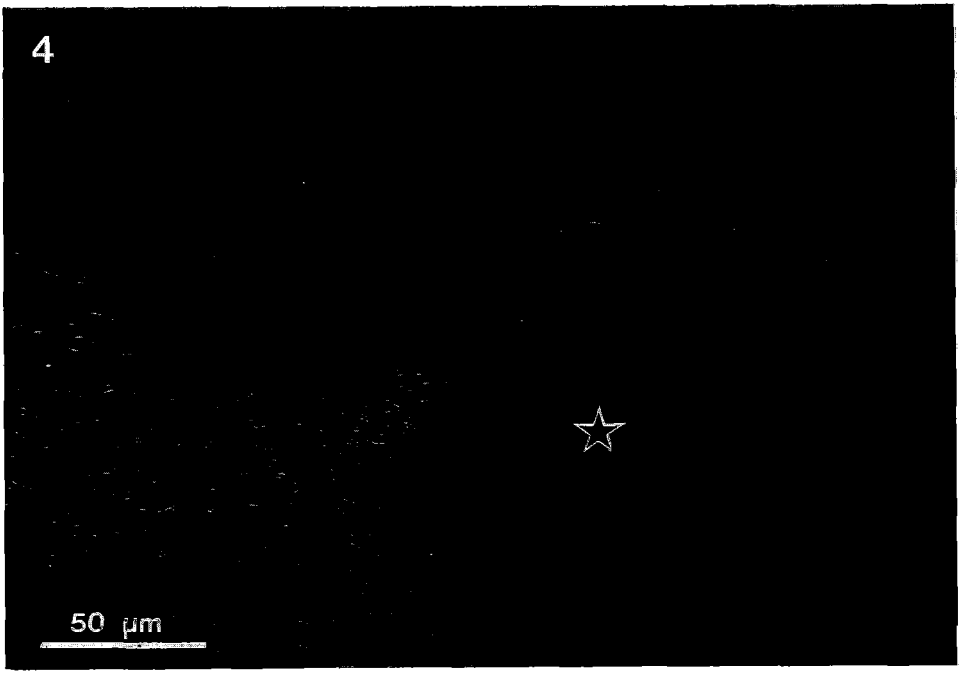
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amorphous capsule-like structure. The structures were found at several places on the surface. They all had a wrinkled aspect and showed vaying outlines (figure 5). Their thickness was always less than 5 micrometers and they were up to 600 micrometers wide. In addition the anterior surface of the lens body was covered with cells, mainly on the part situated inferiorly in the eye. Most of these cells were lying isolated on the surface (figure 6). No other structures could be identified. The lens body itself seemed to be damaged in some places (figures 7 and 8).

2. The loops

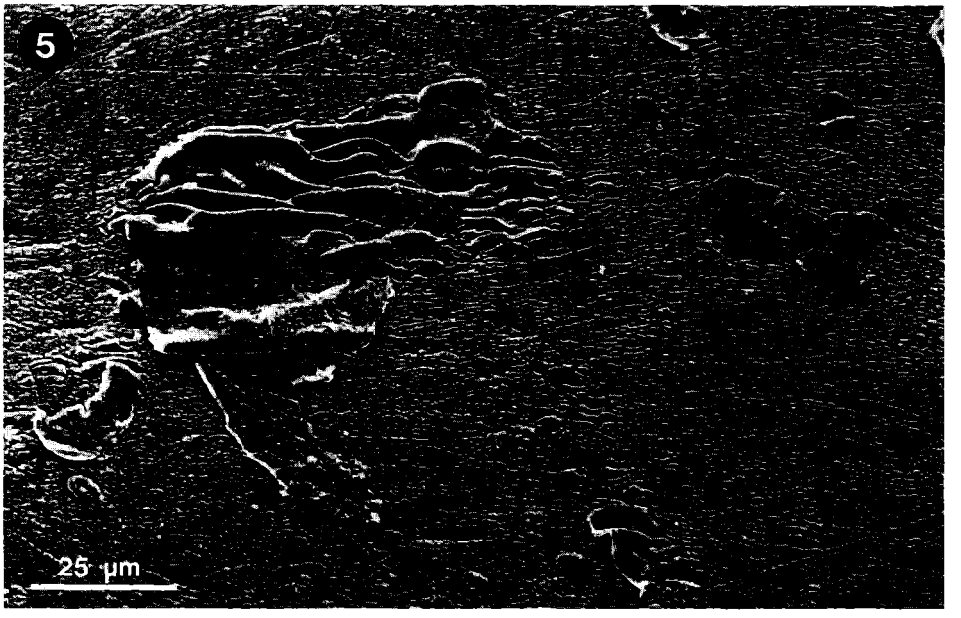
The loops were thoroughly inspected for degenerative changes as described for supramid (polyamide), the material the loops were made of (5). The loops proved to be without any morphologically visible damage. The surface was smooth except for longitudinally running ridges which are most likely due to the manufacturing process. On the loops no adhering cells were present. A peculiar finding was the presence of fibrillar material (figure 9).

3. The suture

The suture, dating from 1972, was carefully studied expecting some biodegradation. However, the thread itself proved to be intact. There were four ends to the suture, two due to cutting during explantation and two which had been cut during implantation. Two loose ends had been in the eye for 12 years and displayed a totally different aspect (figure 10) from the newly cut ends (figure 11). Adhering to the surface of the suture several fibrillar structures could be noticed similar to those found on the loops.

Discussion

Intraocular lenses are manufactured by various methods using various materials. Since Ridley implanted the first IOL in 1949 most IOL lens bodies are made of polymethylmethacrylate (PMMA). The loops of the various types of IOL's were made of polyamide (nylon, perlon, supramid) or polypropylene and after 1979 mostly of polypropylene. An exeption are the one-compound lenses which are made completely of PMMA. The change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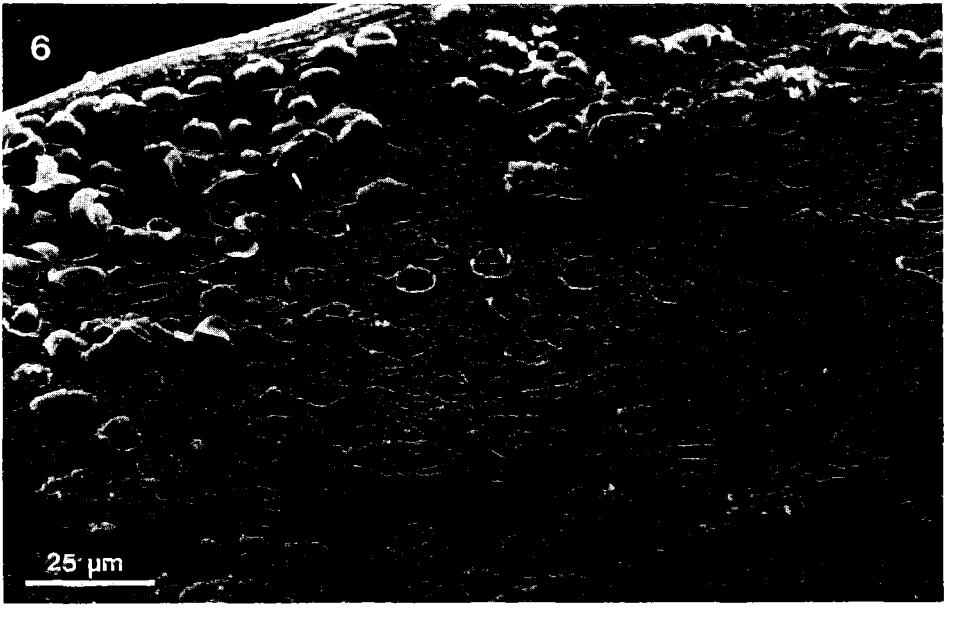
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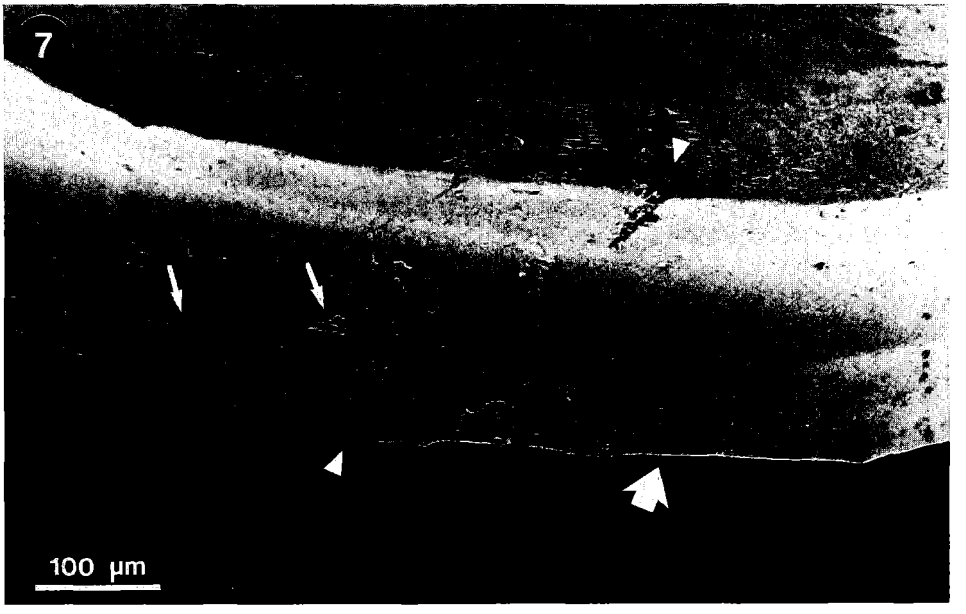
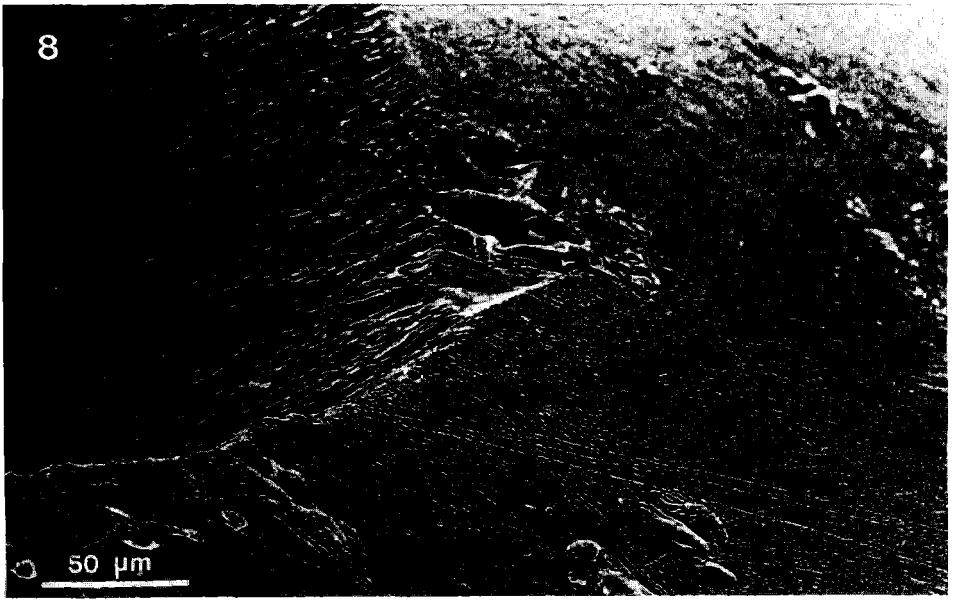
in the use of polyamide to polypropylene was made because of the reports that polyamide showed hydrophilic biodegradation (3).

The manufacturing of intraocular implants mostly includes polishing. In modern IOL's this polishing is done more carefully than in the older ones, resulting in a more smooth-surfaced IOL with more rounded edges. In the case described here, the lens, fabricated in the early seventies, was still in an experimental stage. Therefore it could be expected that this lens had a not so well-polished surface. Obviously this is the reason for the rough surface and the sharp edges of the IOL described in this study. Although imperfect finishing and polishing of IOL edges are believed to be a predisposing factor for several complications, e.g. the uveitis-glaucoma-hyphaema syndrome, in the present case no such complications occured.
The wrinkled membrane-like structures found on both surfaces of the lens were too large to be of cellular origin, even a multinuclear giant cell would not measure 600 micrometers. Remnants of the lens capsule would be thicker than 10 microns and would not be located on both sides of the implant (7). Probably these structures are remnants of the proteinaceous membrane which is described to envelop the IOL after a sequence of events, in order to seperate the implant from the living tissue (8, 9, 10, 11). That only parts of this membrane were found can be caused by the loosening of the implant in spring 1984 or it may be caused by the Strampelli metal thread. It seems remarkable that rupture of this membrane did not cause an inflammatory reaction. This might be a topic for future research.
The cells found on the anterior surface of the lens body are most likely originating from the corneal endothelium. This conclusion is based on previous scanning electron microscopic observations (12, 13) and on the occurrence of the clinically significant intermittent touch syndrome. The damage to the PMMA (figure 7 and 8) may be due to surgical handling during implantation or explantation, as is described before (14).
The fibrillar structures adhering to the surface of the loop have never been previously described. They show some resemblance to zonular fibers (suspensory ligaments of the lens) but we do not have definitive evidence of their nature.

Conclusion

After 12 years of implantation the intraocular lens studied in this paper seemed remarkably unharmed. The rough surface of this early IOL shows how much polishing has been improved over the years. Remnants of a membrane were found in this study on the surface of the lens. Such a membrane has been described in literature (8-11) to envelop the implant after a succesfull acceptation by the host.


7
100 µm


8
50 µm

Acknowledgements

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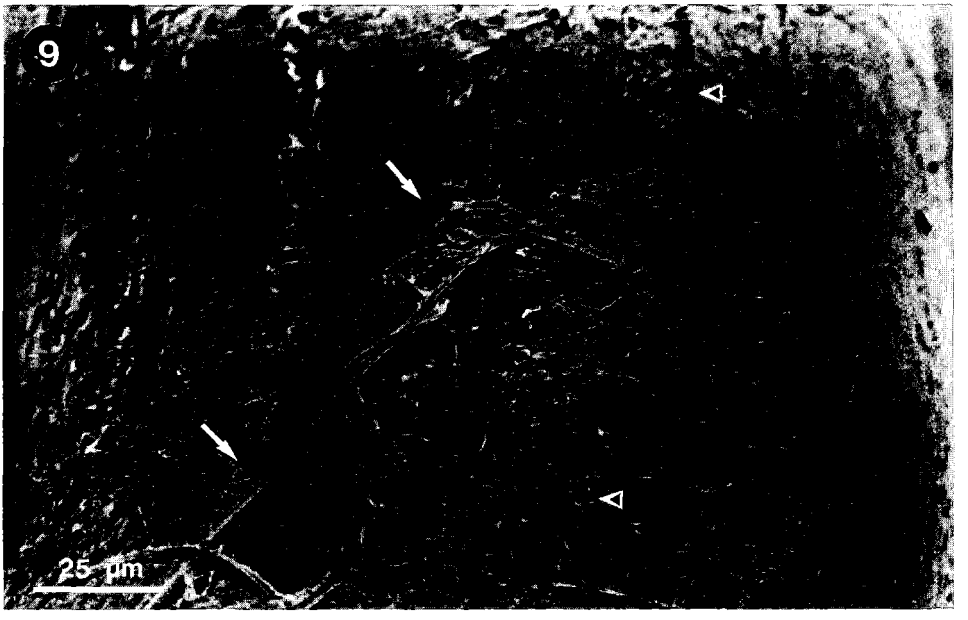
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10
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Legends

Figure 1: In vivo biomicroscopy of the patient's eye prior to the removal of the implant lens (spring, 1984). At the inferior nasal quadrant the cornea displays a scar (arrowhead) and opacifying changes, due to the penetrating injury in 1972 and to the intermittent touch syndrome respectively. Further note the Strampelli threads (arrows).
N: nasal, T: temporal.

Figure 2: Low power SEM picture of the anterior surface of the intraocular lens. Note the temporal suture (T). The central, annular marks (arrowheads) are artificial traces of the conductive carbon cement used in mounting the specimen. Arrow: manipulation holes.

Figure 3: Medium power SEM picture displaying the rough surface of the implant lens. The picture is taken close to one of the manipulation holes (asterisk, compare fig. 2).

Figure 4: Surface of a recent, non-implanted intraocular lens. Note the smooth surface as compared with that of the IOL studied in the present paper (fig. 3). The manipulation hole (asterisk) is most likely frazed out after the polishing process.

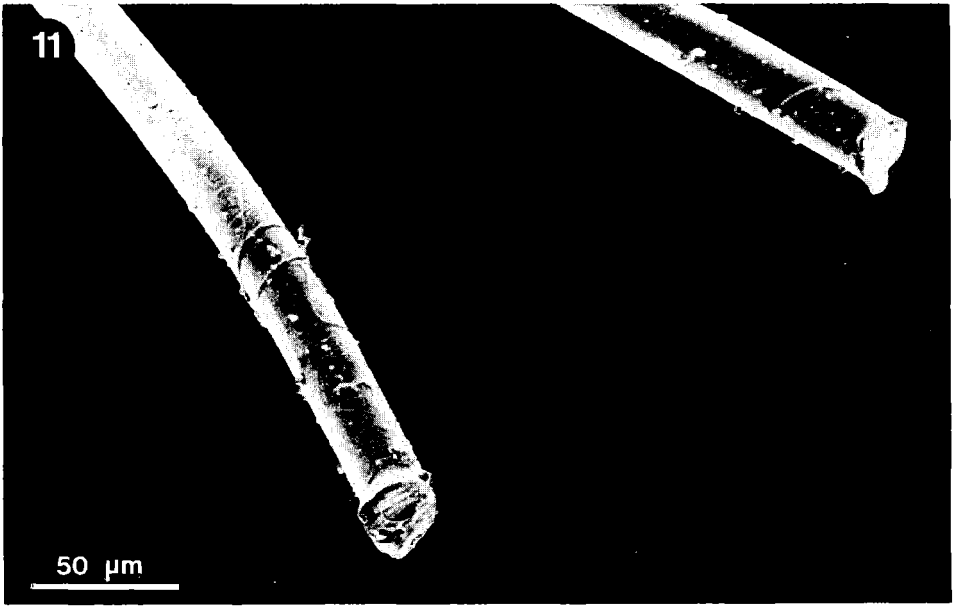
11
50 µm

Figure 5: Membrane-like fragments are found on both sides of the implant. These membrane-like residues are of varying size and have a wrinkled aspect.

Figure 6: Medium power SEM picture illustrating the numerous cellular elelments found at the inferior margin of the implant.

Figure 7: The margins of the intraocular lens are irregular with sharp edges (bald arrow, see also fig. 2). At some places the margin is damaged (arrowheads) and amorphous elements are present (small arrows).

Figure 8: A damaged manipulation hole (see fig. 2) on the anterior side of the IOL. This damage may be due to handling during surgery.

Figure 9: High power view of the supramid loops of the intraocular lens. Note the overall intactness of the loop and the longitudinally running ridges

(arrowheads). A remarkable feature is the presence of fibrillar structures (arrows) on the surface.

Figure 10: High power SEM picture of the perlon's suture which had resided in the eye since 1972. Note the adhering fibrillar elements (arrows) and the rounded tip.

Fig 11: SEM-picture of the two loose ends of perlon's suture cut during explantation. Note the difference in tip shape, indicating that long residence in the eye changes the cut.

5. Discussion

5. Discussion

In this thesis the pathogenesis of after-cataract was studied together with the interaction of the lenticular remnants and intraocular lenses.
The results of the investigations are presented in the preceding chapters together with the respective discussions. However, the various parts of this thesis were written successively and consequently the older parts lack information provided by recent literature. Also some general remarks seem to be due here.
The frequent use of the scanning electron microscope in this thesis invites to some general comments. Scanning electron microscopy gives a high resolution (about 50 nm) three-dimensional view of tissues and cells and is an accepted method in morphological research, provided the tissue is properly fixated and processed. First of all biological materials need to be handled with great care as soft tissues are rapidly torn apart and separate cells are easily washed away. Proper fixation is essential as soon as possible after obtaining the specimens and even after fixation gentle handling remains necessary. The fixative used throughout the studies contained formaldehyde -which is an excellent fixative with a rather slow penetration - and glutaraldehyde, which is an adequate fixative with a fast penetration. The solution was properly buffered with cacodylate. This fixative, described by Peters in 1970, provides excellent fixation for scanning electron microscopy (1). Even then, fixation artifacts can never be ruled out and are possible hazards in interpreting scanning electron microscopic pictures. The next step in the processing is dehydration in a graded series of ethanols. Dehydration causes the tissue to shrink and this varies with the water content of the tissue. Tissue shrinks on an average 26% by ethanol dehydration (2,3). Critical point drying which completes the preparation gives some additional shrinkage and biometric measurements in scanning electron microscopy are therefore unreliable, as is illustrated in chapter 3. Apart from shrinkage the high pressure needed in critical point drying can give some distortion of delicate tissues. Finally the dried specimens are coated with a thin (7 nm) layer of gold. All this implies that artifacts in biological materials can occur because of improper handling, bad fixation, shrinkage or distortion. This is the reason why scanning electron microscopy was combined with transmission electron microscopy and light microscopy in most chapters except for chapter 2.2. In this chapter only separate cells were described together with the wrinkled coating on the anterior surface of implanted intraocular lenses in rabbits. The coating on the lenses had a wrinkled appearance and this wrinkling might well be regarded as an artifact. It can be attributed to shrinkage and it is very likely that in vivo this coating is smooth.
Other undesired side-effects of the preparation procedure for scanning electron microscopy is the occurrence of cracks in the polymethylmetha-

crylate optics of the intraocular lenses and some distortions, as described in chapter 4.3. These deformations might be due to the evaporation of water bound to the polymer molecules.

A morphological description of after-cataract was given in chapter 4.2. In this chapter the epithelial nature of Elschnig's pearls as a major source of opacification of the posterior capsule is described. This might give the false impression that only lenticular epithelium causes posterior capsule opacification. In one specimen (chapter 4.2.) star-shaped cells on the posterior capsule were described apart from the Elschnig's pearls. These cells could originate from fibrous metaplasia of lenticular epithelium as was described by McDonnell, Zarbin and Green (1983) (4) but also from surrounding tissue elements as e.g. from the iris stroma, as was suggested by Hiles (1979) (5). Using immunofluorescent and tritiated thymidine labelling, Odrich et al. (1985) revealed the participation of cells of non-lenticular origin in rabbits (6). Wolter (1985) described in the human the presence of melanocytes on the surface of explanted intraocular lenses together with inflammatory cells (7). Conclusively it can be stated that lenticular epithelium is the main source of opacification of the posterior capsule with a contribution of inflammatory cells, melanocytes and fibroblasts. Especially the non-epithelial factors might be influenced by the direct postoperative reaction.
Special attention should be given to the possible role of the coating which was found on lenses implanted in rabbit eyes (chapter 2.2) and which was suggested to consist of fibronectin. Fibronectin (or cold-insoluble globulin) is a glycoprotein (M=400 to 500 kDalton) that plays a role in many biological activities, as e.g. cellular adhesion and spreading, phagocytosis, cytoskeletal organization and embryonic differentiation (8). Fibronectin was reported to be present in the aqueous humour (9), in tears (10), in the trabecular meshwork cells (11), in corneal endothelial cells (12), in the epithelial basement membrane throughout the entire cornea (13) and more in general in blood plasma, soft connective tissue matrices and most basement membrane systems (14). Fibronectin can assemble into fibrils (8) and it might be that the fibrils between the Elschnig's pearls and the posterior capsule in chapter 4.2. represent fibronectin. In vitro fibronectin is synthesized by many cell types, including fibroblasts, endothelial cells, macrophages, hepatocytes and epithelial cells (14, 15 and 16). M.C. Kenney (1986) described the decrease of fibronectin level in the aqueous of the rabbit after corneal injury (17). It seems very likely that fibronectin influences the postoperative reaction to artificial lens implantationFibronectin might be a connection between the direct postoperative inflammatory reaction in the anterior segment of the eye and the occurrence of after-cataract. The presence of fibronectin in the anterior segment of the human eye and its possible role in after-cataract formation needs further investigation.

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6. Summary

6. Summary

In Chapter 1 an introduction and some statistical data on cataract and cataract surgery are given together with a discussion on the reaction of the eye to an intraocular lens. Techniques for correcting the aphakic refractive error are mentioned followed by a description of the three main types of acrylic intraocular lenses. Main causes for postoperative opacification of the media of the eye are given. At the end of this chapter the aim of this study is explained.

In the first experiment (chapter 2.1.) 25 rabbit eye lenses were extracapsularly extracted without implantation of artificial intraocular lenses. The development of the retained lens material into a Soemmerring's ring during the first 12 months after the operation was studied by scanning and transmission electron microscopy. Three days after the operation the anterior capsular flaps were already sealed to the posterior capsule and the enclosed lenticular epithelium showed cell division and started to differentiate into lenticular fibers. Epithelial cells were found lining the inner side of the anterior capsular flap, scattered in groups along the inner side of the posterior capsule and amidst the fibers in the ring. Only fibrin and fibroblast-like cells but no Elschnig's pearls were present on the central part of the posterior capsule encircled by Soemmerring's ring. The absence of pearls could be explained by the finding that the anterior capsular flap was tightly sealed to the posterior capsule by a fibrinous adherence. This seems to be in contrast with the situation in the human.

In the second experiment (chapter 2.2) extracapsular lens extraction with implantation of an intraocular lens was performed in 14 rabbit eyes. Attention was focussed on the cellular reaction on the anterior surface of the implant during the first three months after the operation. The most remarkable finding was the presence of a thin, wrinkled amorphous coating. It proved that this coating did consist of protein. In an in vitro experiment it was shown that this coating most likely consisted of fibronectin. On the proteinaceous coating macrophages and giant cells were found, their number decreasing with increasing survival time. After a survival time of three months only a few but very large giant cells were found in the manipulation holes and around the sites where the loops were inserted into the optic part of the lens.

The ultrastructure of the human cataractous lens capsule is described in chapter 3, together with the thickness measurements by various morphological methods. The surgically removed anterior segment flaps proved to be covered by epithelial cells and together with the capsule in some instances also cortical material had been removed. Ultrastructurally the capsule see-

med to be bilayered by scanning electron microscopy and homogenous by transmission electron microscopy. Fibrillar areas were only found in one case with Goldmann-Favre disease, a hereditary vitreoretinal degeneration.

In chapter 4.1 the ultrastructure of Soemmerring's ring in 11 human pseudophakic eyes is described. It consisted essentially of the same material as in the rabbit. Enclosed between the anterior capsular flap and the posterior capsule epithelial cells and lenticular fibers in different stages of differentiation and degeneration were found. However, the sealing of the anterior capsular flap to the posterior capsule seemed to be not firm enough to prevent epithelial cells from growing onto the posterior capsule in 9 out of 11 cases. This might have been caused by the intraocular lenses present in all cases. Transmission electron microscopy of the sealing places in three specimens showed inflammatory cells which were not found in the rabbit. Scanning electron microscopy could not identify the presence of fibrin in the human specimens. These two findings might point to a different kind of reaction in the human as compared to the rabbit, the reaction in human being more cellular and in rabbits more fibrinous. The loose appositioning of the anterior capsular flap to the posterior capsule might also be the initiating factor for the development of Elschnig's pearls, described in chapter 4.2. These aberrantly differentiating epithelial cells were shown to contain large, lobulated nuclei and homogenously staining cytoplasm and almost no cell organelles. Also star-shaped cells, resembling fibroblasts, were found on the posterior capsule.

The study of the anterior surfaces of explanted intraocular lenses from humans in chapter 4.3 and 4.4 revealed the presence of macrophages, epitheloid cells and granulocytes. Also flat, round cells were found which were supposed to be corneal endothelial cells. A thin, wrinkled coating around the implant, as in rabbits, was not found. Instead of this continuous coating several fragments of wrinkled, amorphous material were found, which appeared to be thicker than the coating in rabbits. Distortion of the acrylic parts of the intraocular lenses were shown to be caused by the preparation procedure for scanning electron microscopy.

7. Samenvatting

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Na een korte inleiding volgen in hoofdstuk I enige statistische gegevens over cataract of grauwe staar en over cataractchirurgie. De verschillende manieren om de postoperatieve aphakie te corrigeren worden besproken evenals de drie voornaamste typen intraoculaire kunstlenzen. Na een overzicht van de complicaties na cataractchirurgie wordt dieper ingegaan op de hoofdoorzaken van postoperatieve mediatroebelingen als lange-termijn complicatie. Afsluitend volgt een bespreking van het doel van het onderzoek.

In Hoofdstuk 2.1 en 2.2 van dit proefschrift worden twee experimenten beschreven met konijnen waarbij gekeken werd naar de weefselreactie na extracapsulaire lensextractie al dan niet met implantatie van een kunstlens.

In het eerste experiment (Hoofdstuk 2.1) werd extracapsulaire lensextractie uitgevoerd bij 25 ogen van konijnen zonder implantatie van een kunstlens. De ontwikkeling van de lensresten tot een zogenaamde ring van Soemmerring werd bestudeerd m.b.v. scanning en transmissie electronen microscopie tot 12 maanden na de operatie. Drie dagen na de operatie bleek de voorste kapselflap reeds verkleefd te zijn met het achterkapsel en tevens bleek dat het ingesloten lensepitheel delingsactiviteit vertoonde en zich begon te differentieren in lensvezels. De resten van het voorkapsel waren aan de binnenzijde bekleed met epitheel en ook werden verspreide groepjes epitheelcellen aan de binnenzijde van het achterkapsel aangetroffen. Op het centrale, open deel van het achterkapsel werden geen Elschnig'se parels gevonden maar wel fibrine en fibroblast-achtige cellen. De afwezigheid van parels werd verklaard vanuit de fibrineuze verbinding tussen voorkapselflap en achterkapsel die bij mensen veel minder duidelijk aanwezig lijkt.

In het tweede experiment (Hoofdstuk 2.2) werd extracapsulaire lensextractie uitgevoerd bij 14 konijneogen waarbij tevens een achterste oogkamerlens werd geimplanteerd. Bij dit experiment lag de nadruk op de bestudering van de cellulaire reactie op het voorste oppervlak van de kunstlens gedurende de eerste drie maanden na de operatie. De meest opvallende bevinding was de aanwezigheid van een dun, gekreukeld, amorf laagje. Het bleek dat dit laagje wel uit eiwit bestond maar dat het geen collageen betrof. Door vergelijking met een kunstlens die geincubeerd was geweest in een fibronectine-oplossing werd aannemelijk gemaakt dat het hier om fibronectine handelde. Op het boven besproken laagje werden macrophagen en reuscellen aangetroffen, waarbij het aantal ecllen afnam bij toenemende overlevingsduur. Drie maanden na de operatie waren er nog maar enkele, zeer grote reuscellen te vinden in de boorgaten en rond de plaats

waar de poten van de lens in het centrale deel waren bevestigd.

De ultrastruktuur van het voorkapsel van de cataracteuze lens en de diktemetingen hierbij worden beschreven in hoofdstuk 3. De peroperatief verwijderde stukjes van het voorste lenskapsel bleken aan een zijde bedekt te zijn met epitheel en tevens bleken er soms delen cortex meegenomen te zijn. In de scanning electronen microscoop leek het kapsel tweelagig terwijl in de transmissie electronenmicroscoop een homogene struktuur werd waargenomen. Fibrillen werden alleen gevonden in het kapsel van een patient met de ziekte van Goldmann-Favre, een hereditaire degeneratieve retina- en glasvochtaandoening.

In Hoofdstuk 4.1 volgt de opbouw van de ring van Soemmerring in 11 menselijke pseudophake ogen. De lensresten blijken grote overeenkomsten met die bij het konijn te vertonen. Tussen voorkapselflap en achterkapsel bevinden zich epitheelcellen en lensvezels in verschillende stadia van differentiatie en degeneratie. In tegenstelling tot de situatie bij het konijn bleek de verbinding tussen voorkapsel en achterkapsel bij 9 van de beschreven 11 gevallen niet stevig genoeg om epitheelcellen te beletten zich te verspreiden over het achterkapsel. Mogelijkerwijs lag de oorzaak hiervan in de iris-gefixeerde of iridocapsulaire kunstlens die steeds aanwezig was. Transmissie electronen microscopie van de verbindingsplaats tussen voor- en achterkapsel bij drie specimens toonde ontstekingscellen, die niet bij het konijn waren gevonden. Scanning electronen microscopie kon geen fibrine aantonen bij de mens. Deze beide bevindingen wezen in de richting van een verschillende postoperatieve reactie bij mens en konijn, waarbij het konijn een meer fibrineuze reactie en de mens een meer cellulaire reactie vertoonde.

In Hoofdstuk 4.2 worden Elschnig'se parels bij de mens beschreven. Het bleek hier om abnormaal gedifferentieerde lensepitheelcellen te gaan die grote, gelobde keren en een homogeen aankleurend cytoplasma bevatten vrijwel zonder celorganellen. Daarnaast werden ster-vormige cellen op het achterkapsel gevonden die leken op fibroblasten.

De resultaten van scanning electronen microscopie van de voorzijde van kunstlenzen die na een verblijf in het menselijk oog om uiteenlopende redenen werden verwijderd staan in Hoofdstuk 4.3 en 4.4. Er werden macrophagen, epitheloid cellen en granulocyten gevonden naast ronde, platte cellen waarvan vermoed werd dat het endotheelcellen waren. Een dun, amorf laagje rond de kunstlens zoals bij konijnen kon niet worden aangetoond. Wel werden verschillende fragmenten amorf membraneus materiaal aangetroffen, die dikker leken dan de membraan bij het konijn. Vervormingen van de perspex delen van de kunstlenzen bleken te zijn veroorzaakt door de procedure voorafgaand aan de scanning electronen microscopie.

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Curriculum vitae van Johannes Pieter Kappelhof

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