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# IN VIVO DOCUMENTATION OF CELLULAR REACTIONS ON LENS SURFACES FOR ASSESSING THE BIOCOMPATIBILITY OF DIFFERENT INTRAOCULAR IMPLANTS

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## SUMMARY

**This prospective study was undertaken to assess the biocompatibility of different intraocular implants and to determine factors influencing cellular reactions on intraocular lenses (IOLs). Cellular reactions seen on the surface of 653 IOLs have been documented by specular microscopy. Various types of IOLs were used with different surgical procedures in humans. The 11 lens types used fall into five groups of materials: polymethylmethacrylate (PMMA), heparin surface-modified PMMA, surface-modified PMMA, poly Hema and silicone. Factors influencing the cellular reaction on intraocular implants were elaborated on in this study. Besides the foreign-body reaction itself, cellular reactions were influenced by an increased inflammatory disposition, surgical trauma, peri-operative treatment, implant positioning and lens style. A significant correlation was found between the development of posterior synechiae and the existence of giant cells on the anterior lens surface. The incidence of cellular reactions on IOLs revealed significant differences specific to lens and material. Hydrophilic surfaces show cellular reactions in a lower percentage of cases compared with hydrophobic surfaces. An accurate and individual selection of lens material and style is mandatory to guarantee optimal results after surgery.**

With the introduction of different intraocular lens (IOL) materials, styles and surface modifications it has become mandatory to test the biological interaction between the eye and the intraocular implant. *In vitro* and *in vivo* studies have shown that the cellular proliferation on the IOL surface is a good indicator of the biocompatibility of the lens material and of post-operative inflammatory reactions.<sup>1-6</sup> This cellular reaction and its many influencing factors have also been reported.<sup>7,8</sup>

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Specular microscopy allows the *in vivo* examination of cells on the IOL surface.<sup>9-11</sup> With this technique, various types of cells can be observed on IOLs at different times after implantation. The first cells to appear are small round cells that become spindle shaped (spindle-shaped cells) to perform active amoeboid movements and phagocytosis.<sup>4,12-14</sup> Later, epithelioid-like cells and giant cells develop.<sup>4,9,15-17</sup> All these cells are important in assessing the biocompatibility of IOL materials. The number of these cells depends on the IOL material, the degree of post-operative inflammation and the anatomical position of the IOL in the eye.<sup>7,15</sup> These cells, which are derived from blood monocytes,<sup>18</sup> are not the only ones seen on the IOL surface; however, the other cells do not have a great influence on the patient's immune response to the IOL materials.<sup>4</sup>

Specular microscopy was used to perform *in vivo* examinations of 653 implanted IOLs of differing materials, surface modifications and styles, beginning during the early post-operative period and continuing for a mean follow-up of 10 months. Factors influencing the cellular reaction on intraocular implants were identified and an attempt was made to find quantitative and qualitative differences in the cellular reaction on the different IOL materials and styles, respectively.

## MATERIALS AND METHODS

In this prospective study, cellular reactions on 653 IOL surfaces have been documented using specular microscopy after implantation of various lens types in humans. Table I shows the different lens types used, sex and mean age of the patients, and the mean follow-up time for the different groups.

For cataract surgery a standardised technique starting with a scleral tunnel incision was used. After continuous circular capsulorhexis and hydrodissection of the lens,

**Table I.** Patient data

Lens type	Age (years)	n	Follow-up (months)
<i>PMMA</i>			
7 mm PMMA	73 ± 13	84	8.3 ± 2.9
7 mm HSM-PMMA	72 ± 13	50	16.0 ± 4.0
5 mm PMMA	76 ± 6	67	8.2 ± 3.4
5 mm SM-PMMA	78 ± 11	50	5.8 ± 1.5
Sulcus-fixated PMMA	66 ± 18	15	5.3 ± 2.1
<i>Hydrogel</i>			
Poly Hema 1103	75	200	6.0
Poly Hema G triple	77 ± 5	50	13.8 ± 6.6
Poly Hema 1003	79 ± 7	34	9.2 ± 2.9
<i>Silicone</i>			
Silicone disc	76 ± 7	37	15.0 ± 6.0
Silicone phacoflex	76 ± 9	60	7.3 ± 3.4
Total	75	653	9.5

HSM, heparin surface-modified; SM, surface-modified; G triple = glaucoma triple procedure.

phacoemulsification was performed in all cases. Care was taken to place the IOL into the capsular bag. IOLs made of flexible materials (poly Hema and silicone) were folded for implantation using a Faulkner folder. Healon (Pharmacia) was the only viscoelastic material used throughout and the irrigation fluid was also the same in all procedures. In about 40% of patients a self-sealing incision was prepared; the others received radial 10/0 nylon sutures.

In addition to standard cataract surgery, combined cataract–glaucoma procedures were performed in 50 cases (group: poly Hema glaucoma triple). In this group, phacoemulsification and implantation of a folded 1103 poly Hema IOL were combined with trabeculectomy.<sup>19</sup>

In aphakic eyes, sulcus-fixated implants were used (group: sulcus-fixated PMMA). This heterogeneous group consisted of severely injured aphakic eyes and it was necessary to combine complex surgical procedures (vitrectomy, perforating keratoplasty, pupiloplasty, etc.) with the implantation of a sulcus-fixated implant. The exact pathological history and detailed surgical techniques used in this group have been published previously.<sup>20</sup>

The lenses used were made of polymethylmethacrylate (PMMA), heparin surface-modified (HSM) PMMA, surface-modified (SM) PMMA, poly Hema or silicone. Lens types and surface characteristics are listed in Table II. On HSM-PMMA IOLs the heparin molecule is covalently bonded to polyethylenimine, which is electrostatically bonded to PMMA. The surface of SM-PMMA IOLs is molecularly smoothed during the manufacturing process to prevent both protein and cell adhesion. The IOL is made oleophobic, although nothing is added or bonded to the PMMA surface.

In uneventful cases post-operative treatment was standardised and consisted of four times betamethasone and four times indomethacin eyedrops for 4–6 weeks. In patients with increased post-operative inflammation, treatment was adjusted to the individual situation.

For photographic documentation of morphological and cytological findings, a Zeiss non-contact specular micro-

scope was used in all cases. The pupil was dilated and areas of interest on the IOL surface and the anatomical position were examined by specular microscopy. A semi-quantitative method was chosen to estimate the density of small round cells and spindle-shaped cells on the lens,<sup>7</sup> using the scale: +, fewer than 50 cells/mm<sup>2</sup>; ++, fewer than 100 cells/mm<sup>2</sup>; +++, more than 100 cells/mm<sup>2</sup>. This method was compared with a fixed-frame technique, the results being comparable. The exact technique for specular microscopy has already been described in detail.<sup>21,22</sup>

Observation times were the first 3 days, 7 days, 1 month and 6 months post-operatively. A final examination was performed 10 months after surgery. Besides the photodocumentation, accurate drawings with accompanying remarks were made.

For statistical analysis, the Fisher's exact test and the chi-quadrat test were used. A probability value of  $p < 0.05$  was taken to be significant.

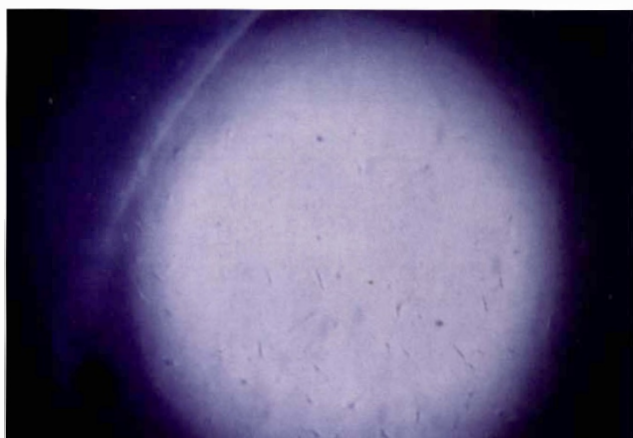
## RESULTS

During the first post-operative days small round cells and spindle-shaped cells were found on all implants (Fig. 1). Where there was increased post-operative inflammation, cell density was higher (Fig. 2). No significant difference was found pertaining to the different implant materials. Table III shows the cell density 7 days after surgery.

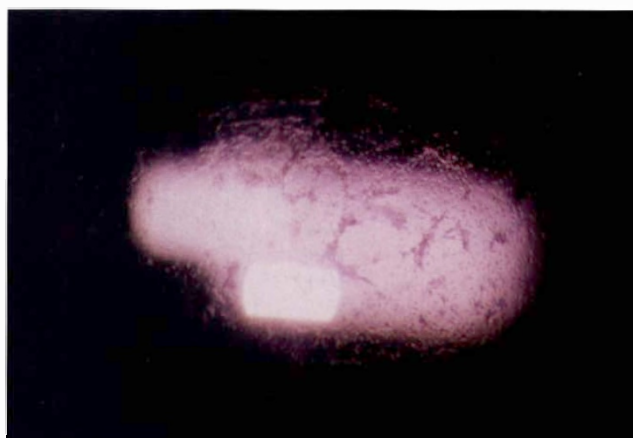
After several days, epithelioid cells and foreign-body giant cells were documented in some cases (Figs. 3, 4). Table IV and Fig. 5 show the results at the final examination. The percentage of foreign-body giant cells varied according to the lens type. These cells were seen most frequently on the silicone disc IOLs. In roughly 27% of cases foreign-body giant cells were seen on 7 mm PMMA, sulcus-fixated and poly Hema 1103 lenses after glaucoma triple procedures. For the 5 mm SM-PMMA IOLs the incidence was 20%. On 5 mm PMMA and on silicone Phacoflex IOLs cellular reactions were found in 14.9% and 16.7% of cases, respectively. The 7 mm HSM-PMMA and poly Hema (1103 or 1003) IOLs had the lowest percentage of cellular reactions. In statistical analysis this difference was significant (chi-quadrat test:  $p < 0.0005$ ) and was caused by the high percentage of foreign-body reactions on 7 mm PMMA, poly Hema glaucoma triple and silicone disc IOLs and by the low percentage on 7 mm HSM-PMMA, poly Hema (1103) and poly Hema (1003) IOLs.

**Table II.** Lens types

Lens type	Material	Surface property
Adatomed 75 ST	PMMA	Hydrophobic/oleophilic
Pharmacia 725 C	HSM-PMMA	Hydrophobic/oleophilic
Pharmacia 740 P	PMMA	Hydrophilic/oleophilic
Optical Radi. Corp. 410 F	PMMA	Hydrophobic/oleophilic
Polytech Poly 5	PMMA	Hydrophobic/oleophilic
Ioptex Smart	SM-PMMA	Hydrophobic/oleophilic
Polytech PC 279 W	PMMA	Hydrophobic/oleophilic
Alcon logel 1103	Poly Hema	Hydrophobic/oleophilic
Alcon logel 1003	Poly Hema	Hydrophobic/oleophilic
Adatomed 90 D	Silicone	Hydrophobic/oleophilic
Allergan SI 26 NB	Silicone	Hydrophobic/oleophilic



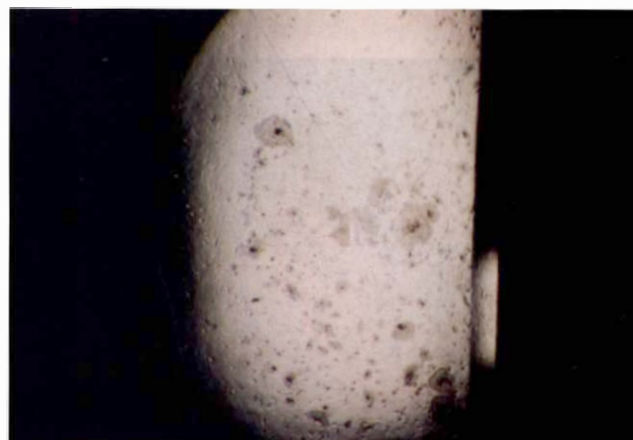
**Fig. 1.** Moderate number of spindle-shaped cells on a poly Hema 1103 IOL. Part of the capsulorhexis is visible. Cell density: <math>< 50 \text{ cells/mm}^2</math>. Original magnification  $\times 130$ .



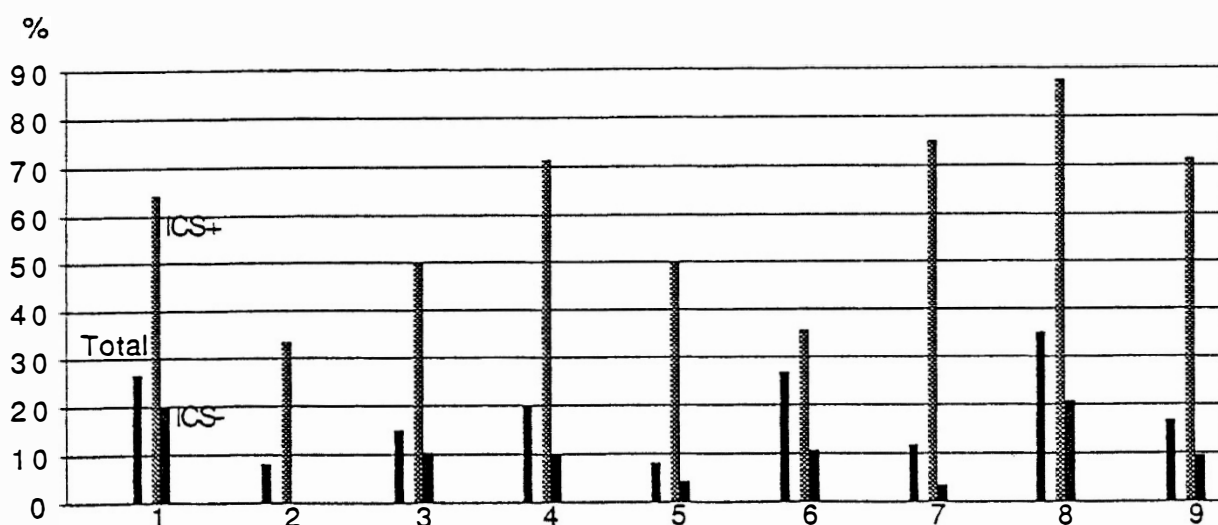
**Fig. 2.** High number of spindle-shaped cells and fibrinous strands on a 7 mm PMMA IOL in a patient with increased post-operative inflammation (diabetes mellitus). Cell density: >100 cells/mm<sup>2</sup>. Original magnification  $\times 40$ .



**Fig. 3.** Foreign-body giant cells with circular formation of spindle-shaped cells on a 7 mm PMMA IOL in a patient with chronic uveitis. Part of the capsulorhexis is visible. Original magnification  $\times 40$ .



**Fig. 4.** Small round cells, spindle-shaped cells, epitheloid cells and foreign-body giant cells on a 5 mm PMMA IOL. Original magnification  $\times 40$ .

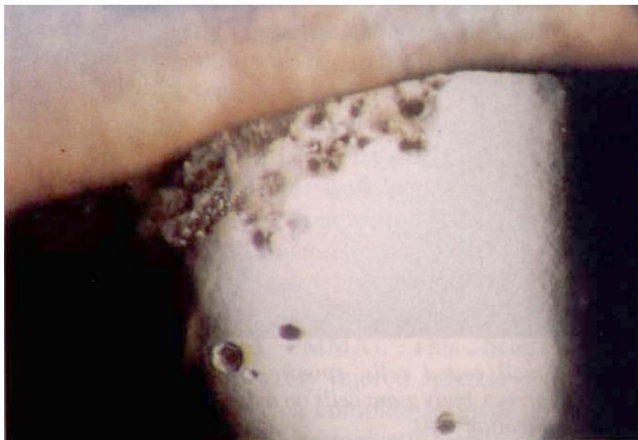


**Fig. 5.** Percentage of foreign-body giant cells on the different intraocular implants at the time of the examination following surgery. 1, 7 mm PMMA; 2, 7 mm HSM-PMMA; 3, 5 mm PMMA; 4, 5 mm SM-PMMA; 5, Poly Hema 1103; 6, Poly Hema glaucoma triple; 7, Poly Hema 1003; 8, Silicone disc; 9, Silicone phacoflex. ICS+, all cases with iridocapsular/iridolenticular synechiae; ICS-, all cases without iridocapsular/iridolenticular synechiae.

**Table III.** Cell density of small round cells and spindle-shaped cells on the different IOLs observed 7 days after surgery

	Uneventful case	Increased inflammation
<i>PMMA</i>		
7 mm PMMA	+ / ++	+++
7 mm HSM-PMMA	+ / ++	+++
5 mm PMMA	+ / ++	+++
5 mm SM-PMMA	+ / ++	+++
<i>Hydrogel</i>		
Poly Hema 1103	+ / ++	+++
Poly Hema 1003	+ / ++	+++
<i>Silicone</i>		
Silicone disc	+ / ++	+++
Silicone Phacoflux	+ / ++	+++

+, fewer than 50 cells/mm<sup>2</sup>; ++, fewer than 100 cells/mm<sup>2</sup>; +++, more than 100 cells/mm<sup>2</sup>.

**Fig. 6.** Foreign-body giant cells on a 7 mm HSM-PMMA IOL. Iridocapsular synechia is visible at the area of cellular invasion. Original magnification  $\times 40$ .

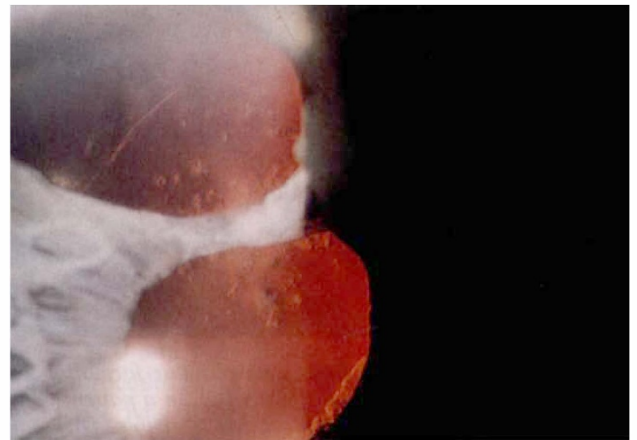
It was demonstrated in all lens groups that those patients with iridocapsular or iridolenticular synechia showed a significantly higher incidence of foreign-body giant cells than those without posterior synechia (Fig. 6). The 7 mm PMMA, 5 mm SM-PMMA, poly Hema (1003), silicone disc, and silicone Phacoflex IOLs showed an occurrence rate of posterior synechia and cellular reactions on the lens surface of over 64%. The equivalent value was 50% for 5 mm PMMA and poly Hema (1103) IOLs, while 7 mm HSM-PMMA and poly Hema (1103) IOLs (glaucoma triple) showed a combined occurrence of less than 36%. Sulcus-fixated PMMA implants were sutured at some distance from the iris, so that they did not show synechia formation and thus were excluded from this statistical calculation. On statistical analysis the difference between the groups was not significant (chi-quadrat test:  $p < 0.11$ , Fisher test:  $p < 0.11$ ).

As expected, in cases with no posterior synechia, sul-

**Table IV.** Percentage of foreign-body giant cells and posterior synechia on the different intraocular implants at the last visit

	Foreign-body giant cells (%)			
	Total	ICS/ILS+	ICS/ILS-	Select. ICS/ILS
<i>PMMA</i>				
7 mm PMMA	26.6	64.3	19.7	16.4
7 mm HSM-PMMA	8.0	33.3	0	0
5 mm PMMA	14.9	50.0	10.2	7.0
5 mm SM-PMMA	20.0	71.4	10.0	7.3
Sulcus-fixated PMMA	26.7	0	26.7	-
<i>Hydrogel</i>				
Poly Hema 1103	8.0	50.0	4.3	1.9
Poly Hema Gl triple	26.9	35.5	10.5	-
Poly Hema 1003	11.7	75.0	3.3	0
<i>Silicone</i>				
Silicone disc	35.1	87.5	20.7	17.9
Silicone Phacoflux	16.7	71.4	9.4	9.4
Statistical results:				
Chi-quadrat test: $p <$	0.0005	0.11	0.0005	0.0005
Fisher test: $p <$		0.11		0.00015

ICS/ILS+, all cases with iridocapsular/iridolenticular synechia; ICS/ILS-, all cases without iridocapsular/iridolenticular synechia; Select., all cases without pre-existing factors influencing the inflammation after surgery and without ICS/ILS.

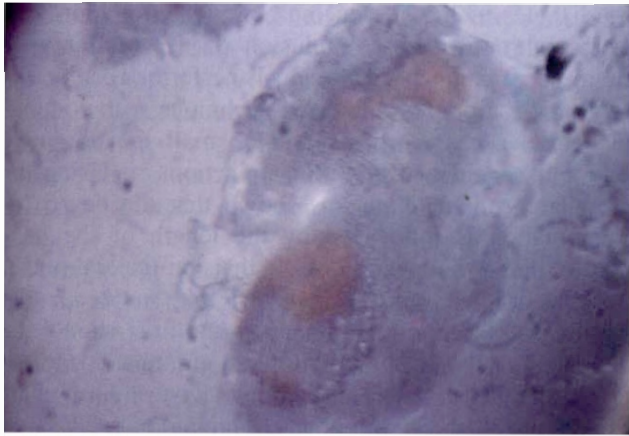
**Fig. 7.** Foreign-body giant cells on a poly Hema 1103 IOL in a glaucoma triple case. The cells migrate onto the IOL surface from both sides of the iridolenticular synechia. Original magnification  $\times 16$ .

cus-fixated PMMA implants showed the highest incidence of cellular reactions on the IOL surface, followed by the 7 mm PMMA and silicone disc IOLs (approx. 20%).

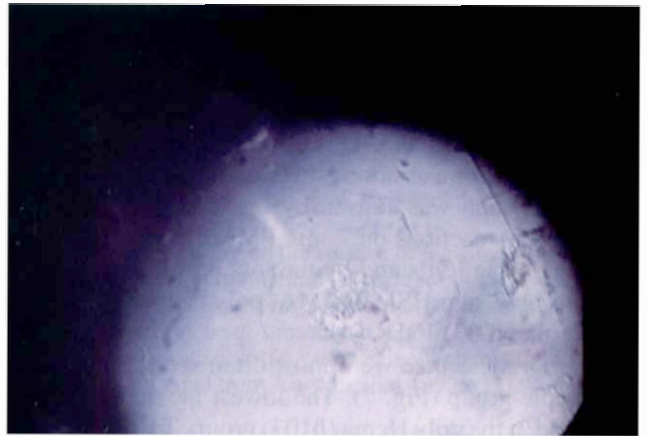
In roughly 10% of cases foreign-body giant cells were documented on 5 mm PMMA, 5 mm SM-PMMA, poly Hema (1103) (glaucoma triple) and silicone Phacoflex IOLs. Poly Hema IOLs showed a very low percentage of these cells and the 7 mm HSM-PMMA IOLs exhibited no cells at the last examination. This difference was statistically significant (chi-quadrat Test:  $p < 0.0005$ ) and due to the high percentage of foreign-body reactions on 7 mm PMMA, sulcus-fixated PMMA and silicone disc IOLs and to the low percentage of such reactions on 7 mm HSM-PMMA, poly Hema (1103) and poly Hema (1003) IOLs.

Excluding all patients with pre-existing factors influencing inflammation after surgery (diabetes mellitus, glaucoma, pseudoexfoliation syndrome, chronic uveitis, occlusion of the central vein, intumescent cataract,

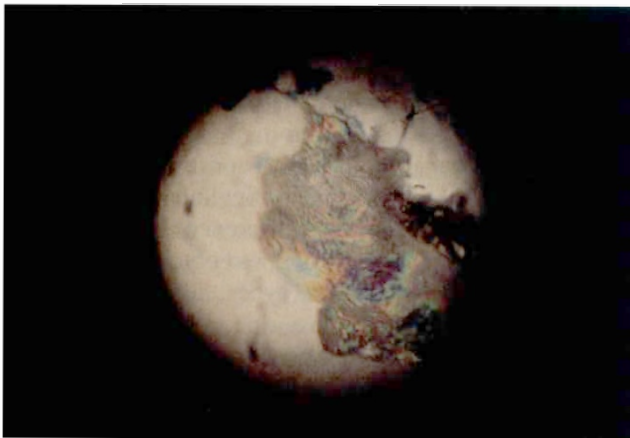




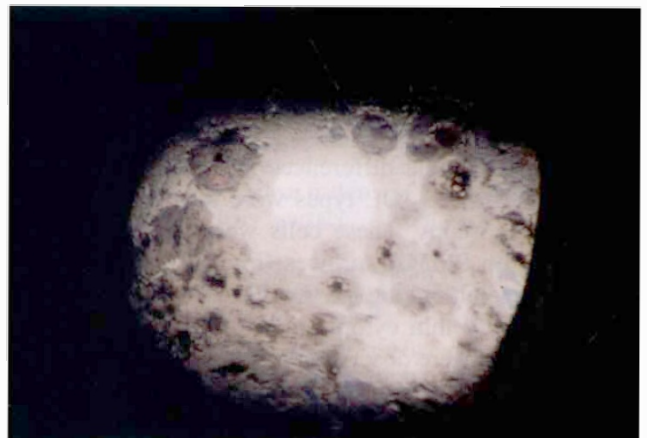
**Fig. 8.** Two large foreign-body giant cells ( $>500 \mu\text{m}$ ) with a high number of nuclei and vacuoles on a 7 mm PMMA IOL. Original magnification  $\times 200$ .



**Fig. 9.** Foreign-body giant cell with thin cytoplasm, vacuoles and nuclei on a 5 mm PMMA IOL. Original magnification  $\times 130$ .



**Fig. 10.** Foreign-body giant cell with Newton's rings on a 7 mm PMMA IOL. Original magnification  $\times 130$ .



**Fig. 11.** Membrane-like formation of foreign-body giant cells on a 7 mm PMMA IOL in a case of chronic uveitis. Original magnification  $\times 25$ .



**Fig. 12.** Membrane of foreign-body giant cells. One cell exhibits an intracellular pigment granule. Original magnification  $\times 130$ .

previously performed ocular surgery or radiation), the percentage of cellular reactions was somewhat lower than when only those cases with posterior synechiae were excluded. After this exclusion, no cells were detected on poly Hema (1003) IOLs. This difference was statistically significant (chi-quadrant test:  $p < 0.0005$ , Fisher test:  $p < 0.00015$ ) and was caused by the high percentage of foreign-body reactions on 7 mm PMMA and poly Hema glaucoma triple IOLs and by the low percentage of such reactions on 7 mm HSM-PMMA, poly Hema (1103) and poly Hema (1003) IOLs.

Posterior synechiae were most often seen in the glaucoma triple group (Fig. 7). The lowest incidence (9.5%) was found in the poly Hema (1103) group. This difference was statistically significant (chi-quadrat test:  $p < 0.0005$ ). The highest percentage of posterior synechia formation was found in the poly Hema glaucoma triple group, the lowest percentage in the poly Hema (1003) group.

In all groups, the percentage of cellular reactions was significantly higher in those cases exhibiting posterior synechiae (chi quadrant test:  $p < 0.05$ ).

Using specular microscopy to examine small round cells and spindle-shaped cells no significant morphological differences were found between the various lens groups.

The morphological differences in foreign-body giant cells on the various IOL types were also studied using specular microscopy. These cells were generally larger ( $> 500 \mu\text{m}$ ) on PMMA surfaces (Fig. 8) than on HSM-IOLs, poly Hema or silicone. On PMMA, the cells often exhibited a very thin cytoplasm with vacuoles (Fig. 9). Newton's rings were observed on some of all of the various lens types (Fig. 10), indicating a thin membrane on the IOL surface. These colourful fringes were created by the thin cellular cytoplasm or by acellular membranes, which cause interference of the reflected light.<sup>23</sup>

Membrane-like formations of foreign-body giant cells on the IOLs were sometimes documented on PMMA, poly Hema or silicone (Figs. 11, 12). In almost all cases these membranes were located close to the posterior synechiae. However, no morphological differences specific to the lens type or material were found when analysing membrane formation of foreign-body giant cells.

## DISCUSSION

Factors influencing the cellular reaction on intraocular implants have been presented in previous studies<sup>7,8</sup> and are further supported by this prospective study. There is a direct correlation between the degree of post-operative inflammation and the degree and percentage of cell reactions.<sup>1,3,7-9</sup> In cases of increased post-operative inflammation, cell density of small round cells and spindle-shaped cells was higher in all groups.

In addition to the foreign-body reaction, cellular reactions are influenced by an increased inflammation disposition, trauma during surgery, peri-operative treatment, anatomical position of the implant and lens style.<sup>3,7,8</sup> Pre-operative factors influencing the cellular reaction on IOLs

are diabetes mellitus, glaucoma, pseudoexfoliation syndrome, chronic uveitis, occlusion of the central vein, intumescent cataract and previously performed ocular surgery or radiation.<sup>7,8,24</sup> A surgical technique with continuous circular capsulorhexis and a small incision may reduce the incidence of cellular reactions.<sup>7,25</sup> Using the laser-flare cell meter it was shown that the degree of inflammation is influenced by the length of the incision.<sup>26,27</sup> Even the location of the incision (scleral tunnel incision or clear cornea incision) may influence the results. Intra-operative trauma to the iris should be avoided. Lens style should allow an atraumatic implantation<sup>3</sup> and the lens surface should not have any irregularities. Here, chemical and physical properties of the lens surface play a major role.<sup>28</sup>

The formation of posterior synechiae may be provoked by increased post-operative inflammation with and without fibrin, post-operative flattening of the anterior chamber, inadequate lens positioning and flaps of the anterior capsule when using a 'can-opener' capsulotomy.<sup>7</sup>

A significant correlation between the development of posterior synechiae and the existence of foreign-body giant cells on the anterior lens surface was found. In cases with iridocapsular or iridolenticular synechiae resident macrophages of the iris stroma may move onto the lens surface.<sup>12,5-17,29</sup> Posterior synechiae constitute a risk factor with respect to the development of cellular reactions.

Quantitative and qualitative differences specific to lens and material were found. In order to obtain valid results when comparing different lens types, all cases with pre-existing risk factors and posterior synechiae must be excluded.<sup>7</sup> Only selected cases using the same surgical technique and the same peri-operative treatment should be used to reach conclusions on the biocompatibility of IOLs.

The percentage of foreign-body giant cells on the different lens types varied significantly. On PMMA lenses, cells were documented most frequently in cases with injured eyes receiving a sulcus-fixated implant. Due to the inflammatory disposition and the increased trauma during surgery, this result was expected. Another reason is an effect on the blood-aqueous barrier of the sutured haptic, as it is in constant contact with uveal tissue.<sup>30</sup> On small-optic PMMA IOLs cells were seen less often than on 7 mm optic PMMA IOLs. This could be explained by the fact that smaller incisions show less inflammation post-operatively. studies with the laser-flare cell meter have demonstrated this effect.<sup>26,27</sup> No significant difference could be found between 5 mm PMMA and 5 mm SM-PMMA IOLs. HSM implants had cells less frequently than the other PMMA IOLs. As shown in other studies on biocompatibility, a hydrophilic IOL surface seems preferable to hydrophobic or oleophobic surfaces.<sup>1,9,31</sup>

Low percentages of foreign-body giant cells were found on the poly Hema IOLs, with both poly Hema lens styles showing similar results. This underlines the sensitivity of the evaluation technique. Cellular reactions were seen more often in glaucoma triple procedure cases with implantation of a poly Hema IOL than in those with stan-

ard cataract surgery and implantation of the same lens type. After glaucoma triple procedures, the formation of posterior synechiae was significantly higher than after simple cataract procedures alone. The high incidence of synechiae in this group was caused by a glaucoma-induced disposition, increased intra-operative trauma (iridectomy, scleral flap), and flattening of the anterior chamber.<sup>19</sup>

Foreign-body giant cells were found more often on silicone disc IOLs than on three-piece silicone IOLs. This can be attributed to the lens style and the resulting increase in traumatization of ocular tissue during implantation.<sup>3</sup>

Hydrophilic lens surfaces showed a lower frequency of foreign-body giant cells than hydrophobic lens surfaces. We therefore believe that hydrophilic IOL surfaces suggest a higher biocompatibility. Chemical and physical properties of the lens surface play a major role in influencing the foreign-body reaction.

Pigment deposits were found more frequently on hydrophobic surfaces.<sup>9</sup> This may be explained by the reduced invasion of cells resulting in reduced phagocytosis of the pigment by macrophages.<sup>9</sup>

Morphological differences in the foreign-body giant cells on the various lens types were also documented. On PMMA, cells were usually flatter and larger than on HSM- and SM-PMMA, poly Hema or silicone surfaces. Newton's rings were created by a cellular lamella or an acellular proteinaceous membrane. Newton's rings develop because of the interference of light reflected from interfaces of materials with different refractive indices.<sup>23</sup> This phenomenon was observed on all lens types.

Experimental studies have shown that a dense membrane of foreign-body giant cells may reduce visual acuity.<sup>32,33</sup> If the cellular membrane cannot be reduced by conservative antiphlogistic treatment, YAG laser abrasion is a low-risk therapeutic alternative.<sup>33</sup> Evidence of reduced contrast sensitivity and glare disability resulting from moderate cellular invasion could not be found.<sup>34</sup>

The clinical results of the different lens types were comparable to those found in previous studies.

*In vivo* studies of cellular reactions on lens surfaces allow important conclusions concerning the pathophysiology after lens implantation. Strict guidelines are necessary to obtain valid results. The *in vivo* documentation of cellular reactions is an important method of assessing the biocompatibility of different intraocular implants with high sensitivity and high specificity.

Key words: Biocompatibility, Foreign-body giant cells, Intraocular lenses, Polymethylmethacrylate (PMMA), Silicone, Specular microscopy.

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