

## Latest Concepts Regarding the Natural Course and Treatment of Post-implant-surgical-inflammation

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### Introduction

Current advances in surgical technique, improved biocompatibility of intraocular lenses (IOLs), and improved postoperative anti-inflammatory agents, have resulted in great reductions in the usual postoperative inflammation. Even so, physiological reactions to surgical trauma and the implantation of a foreign body such as an intraocular lens (IOL) are unavoidable. Biological inflammation is affected by numerous factors, including the surgical procedure, postoperative anti-inflammatory treatment, type of agents used during and after the surgery, biocompatibility of the IOL, and race of the patient. Secondary cataracts have also come to be considered one type of postoperative inflammatory reaction, or as a reaction of the lens epithelial cells to the healing of the wound.

Given this, postoperative inflammation is commonly used today as an indicator in the analysis of various factors including those mentioned above, and for evaluation of the postoperative anti-inflammatory treatments.

The present paper first offers an overview of past and present research into postoperative inflammatory reactions and their significance. This is followed by a brief summary of clinical postoperative inflammation, with particular emphasis on the period of onset.

### Postoperative Inflammation

#### Physiological Basis for the Inflammatory Response

The inflammatory response is essentially a response to various external stimuli, and is thought to be the first line in a series of biological defense mechanisms. This response has long been known to be the beginning of the process of healing in body wounds, and in this sense it is a positive physiological response. If excessive, however, it can be damaging. Such an excessive reaction may be included among the postoperative reactions that follow the implantation of IOLs, which are discussed in the last part of the paper. These excessive, damaging reactions, however, have become rare in recent years, and can now fortunately be written about mostly from a historical perspective. The following is a brief discussion of the fundamental aspects of postoperative inflammation, including a look at the molecular biology involved.

Figure 1. Signal exchange and amplification systems in early stage of inflammation

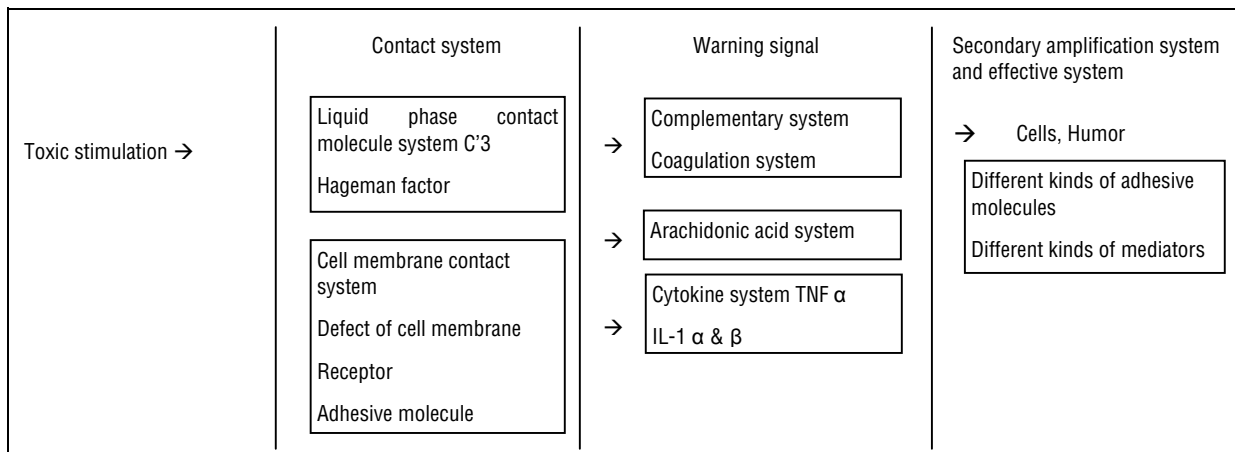


Figure 1<sup>1</sup> shows the mechanisms that first serve to translate the various surgical stimuli acting on the anterior chamber, anterior uvea, and lens for the biological systems involved. Two types of stimulation, that from the surgical procedure itself and from the drugs used intraoperatively, cause the first changes in the contact system. These changes are thought to occur either through C'3 or Hageman factor in the liquid phase contact molecule system, or by direct transmission of the surgical or drug stimuli to the cell membrane contact system.

Primary stimuli acting on these 2 contact systems then produce a warning signal, which transmits these stimuli to the body's defense system. The substances that transmit this signal may be connected to the complement system, kinin system, coagulation system, various amines, arachidonic acid cascade products, lysosomal enzymes, cytokines, and/or endothelin. In fact, these chemical transmitters continue to interact as postoperative inflammation

progresses. In most cases of IOL implantation surgery today, however, these inflammatory reactions remain within the bounds of normal physiological reactions and do not continue past a certain period of time.

The author conducted several studies on the severity of postoperative physiological inflammation by applying various amounts of the above chemical transmitters. When polymethyl methacrylate (PMMA), the main material used in IOLs today, is replaced with polypropylene, the complement system is not as readily activated.<sup>2,3</sup> Lysosomal enzymes in the aqueous humor have been reported to decrease with the preoperative administration of nonsteroidal anti-inflammatory drugs such as indomethacin.<sup>4</sup> The role of cytokines in postoperative inflammation has also become a matter of some interest. Clinical studies have shown that there is a certain period in which the cytokines interleukin 6 and interleukin 1 *K* act in postoperative inflammation.<sup>5,7</sup> A very great number of studies have been done on prostaglandin, the product of the arachidonic acid cascade, which is discussed in the following.

### Postoperative inflammation and the arachidonic cascade: Prostaglandin

In 1965, Ambache et al. discovered that a substance called irin was biosynthesized following injury to the anterior chamber.<sup>8</sup> They reported that this substance was related to the ciliary injection that occurs following injury to the anterior chamber, increases in protein or cells in the aqueous humor, or miosis.<sup>8</sup> It was later discovered that irin was in fact prostaglandin, which is biosynthesized in the arachidonic acid cascade.

The arachidonic acid cascade has 2 pathways (Figure 2). In one of these, prostaglandin is biosynthesized as a product of cyclooxygenase. Nonsteroidal anti-inflammatory drugs have been studied as one type of cyclooxygenase inhibitor, and have been found to prevent the occurrence of various reactions resulting from surgical stimulation to the anterior chamber.<sup>9</sup> Moreover, ocular absorption has been shown to be better with eyedrops than with general administration of nonsteroidal anti-inflammatory drugs.<sup>10,11</sup>

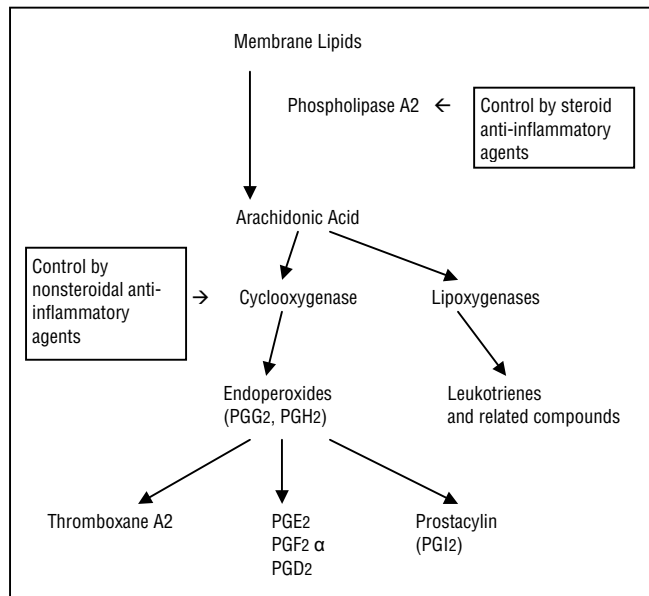


Figure 2. Arachidonic acid cascade

In the late 1970s, the first nonsteroidal anti-inflammatory eyedrops were tried by Sawa and Masuda in Japan.<sup>12</sup> These were indomethacin eyedrops used during soft cataract aspiration to prevent miosis. Shortly thereafter, Miyake reported that it was possible to prevent cystoid macular edema following lens extraction.<sup>13,14</sup> Also during this period, Miyake and Mochizuki et al. discovered that the same nonsteroidal anti-inflammatory drugs prevented postoperative inflammation and the breakdown of the blood-aqueous barrier.<sup>14,15</sup> In the 20 years since that time, nonsteroidal anti-inflammatory drugs have come to be used worldwide for the prevention of postoperative inflammation.<sup>16</sup>

Common intra- and postoperative inflammatory reactions include the above-mentioned intraoperative miosis, postoperative iridocyclitis, inflammatory blood-aqueous barrier breakdown, CME, and inflammation of the fibrinoid pupillary membrane. Such inflammatory reactions can be inhibited with the use of nonsteroidal anti-inflammatory drugs; with recent surgical techniques and IOLs, various nonsteroidal anti-inflammatory drugs are now able to completely inhibit postoperative inflammation for 1-3 months. Debate remains, however, as to whether these drugs are effective against established chronic CME.

### Determination of postoperative inflammatory blood-aqueous barrier breakdown and its clinical application

Clinical quantification of the extent of damage to the blood-aqueous barrier is possible today thanks to the development of the fluorophotometer and laser flare cell meter.<sup>17,18</sup> Moreover, since the laser flare cell meter is easy to use and non-invasive, the blood-aqueous barrier can be repeatedly measured following surgery, and the measurements used as physiological or clinical indicators.

Conventional indicators of physiological inflammatory breakdown of the blood-aqueous barrier include postoperative assessment and size of the anterior capsular incision following intracapsular cataract extraction (ICCE), extracapsular cataract extraction (ECCE), and phacoemulsification and aspiration (PEA), as well as comparisons of the intra- and extracapsular fixation of IOLs.<sup>19</sup> Viscoelastic substances, carbonic anhydrase inhibitors, antiphlogistics, and intraocular perfusions have all been tested as indicators of the severity of postoperative inflammation, to be used in evaluating the instruments or drugs used in surgery.

Table 1. Amounts of Prostaglandin E2 in the Aqueous Humor of Eyes of Baboons with No Complications\*

Prostaglandin E, amount, ng/L				
	Group 2 (PEA)	Group 3 (PEA, PCL)	Group 4 (PEA, PCL, indomethacin)	Group 5 (PEA, PCL, betamethasone)
<b>Postoperative Day 1</b>				
	57	840	147	600
	42	332	42	243
	33	155	57	2,990
	172	309	82	1,325
Mean ± SD	76.00±32.38	409.00±148.94+	82.00±23.18‡	1,289.50±609.89
<b>Postoperative Day 8</b>				
	606	7,020	146	9,000
	698	2,670	87	8,030
	219	10,470	63	8,690
	245	...	...	...
Mean ± SD	442.00±122.80§	6,720.00±2,256.66+	98.67±24.66‡	8,573.33±286.03§

\*All subjects in Group 1 (control) had values of 25 or less. Groups 2-5 all had significantly high values ( $p < 0.01$ ).

PEA: phacoemulsification and aspiration; PCL: posterior chambers lens. Leukotriene B4 was not detected in these groups. + $p < 0.05$  compared to Group 2. ‡ $p < 0.5$  compared to Groups 3 and 5. § $p < 0.5$  compared to postoperative Day 1. (Adapted from ref. 24)

Table 2: Amounts of Prostaglandin E2 in the Aqueous Humor of Eyes of Baboons with Complications

Group	Leukocytes ( $10^9/L$ )	Protein (g/L)	Prostaglandin E2 (ng/L)	Leukotriene B4 (ng/L)	Diagnosis/Bacterial cause
PEA, PCL	-	40.53	88.500	<417	Anterior chamber bleedings
PEA, PCL Indomethacin	12.90	18.93	>250,000	1,770	Endophthalmitis Staphylococcus epidermidis
	36.40	15.74	98,700	2,700	Endophthalmitis Staphylococcus epidermidis
	21.30	4.80	1,952	<417	Endophthalmitis Staphylococcus epidermidis
PEA, PCL Betamethasone	12.00	29.73	64,200	2,003	Endophthalmitis Staphylococcus epidermidis

PEA: phacoemulsification and aspiration, PCL: posterior chamber lens. (Adapted from ref. 24)

Inflammatory breakdown of the blood-aqueous barrier is also used in studying the biocompatibility of various IOLs<sup>20</sup> and the differences in inflammatory breakdown of the blood-aqueous barrier among different races,<sup>21,22</sup> not only in the eye which has been operated on but also in the contralateral eye through so-called consensual reaction,<sup>23</sup> as discussed below.

#### Postoperative inflammation: one aspect of secondary cataracts (capsular opacity)

Recent findings have suggested that some cases of secondary cataracts include an inflammatory reaction. Since the lens capsule is made of collagen type 4, Miyake et al. compared the capsular opacity and postoperative inflammation after fitting PMMA IOLs and collagen type 4 IOLs intracapsularly,<sup>20</sup> and found that the eyes receiving the collagen type 4 IOL implants had less postoperative inflammation and anterior capsule opacity.<sup>20</sup> They showed in another that baboon eyes in which PMMA IOLs were attached in the lens capsule had greater amounts of prostaglandin E2 in the anterior chamber on postoperative days 1 and 8 (Tables 1 & 2).<sup>24</sup> Prostaglandin E2 and interleukin 1 were shown by Nishi et al. to be biosynthesized within the culture medium in a line of cultured lens epithelial cells.<sup>7</sup> It was also found by Tsuboi et al. that flare was greater in the early postoperative stage in eyes in which the IOL was attached intraocularly than in those in which it was attached extraocularly, and that the flare was also greater with smaller diameter continuous curvilinear capsulorhexis (CCC).<sup>25</sup>

Thus, pseudometaplasia may be caused by the contact of lens epithelial cells with the biomaterial of IOLs, for example PMMA, which leads to the biosynthesis of inflammatory mediators. If so, and since pseudometaplasia occurs in lens epithelial cells, 2 investigative indicators of bio-compatibility that can be detected clinically may be suggested. These are anterior capsule opacity and postoperative inflammatory breakdown of the blood-aqueous barrier (Figure 3).<sup>20</sup> The main cause of postoperative inflammation was long considered to be the surgical wound or certain types of immune reaction, but this inflammation is now known to be also involved in the healing mechanism for wounds to lens epithelial cells and pseudometaplasia. Miyake et al. therefore compared several types of foldable IOLs, and found less inflammatory breakdown of the blood-aqueous barrier, less anterior capsule opacity, and a more gradual development of inflammation with IOLs having a greater surface hydrophilicity.<sup>26</sup>

**Types of Pathological Postoperative Inflammation and their Periods of Onset**

In this last section I would like to briefly discuss the symptoms and period of onset of the various types of postoperative inflammation requiring clinical treatment, as summarized in Table 3.<sup>27</sup>

All the conditions mentioned in this table are inflammations due to excessive bacterial toxins, immune response, or response to foreign substances, including postoperative bacterial endophthalmitis, toxic lens syndrome, and uveitis-hyphaema-glaucoma (UHG) syndrome. Referring to Figure 1, it is seen that there is excessive triggering of the amplification system described above.

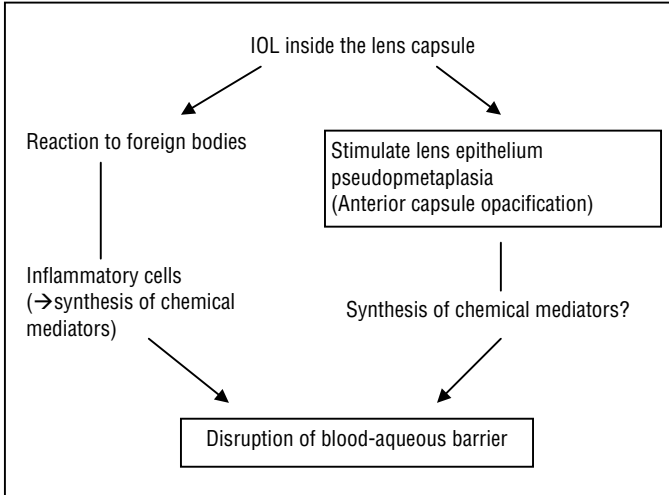


Figure 3. Working hypothesis on blood-aqueous barrier function and lens epithelium pseudometaplasia as indicators of the biocompatibility of IOLs (Adapted from ref. 20)

This is shown, for example, in the baboon experiments of Miyake et al., in which all baboons with inflammation inside the normal physiological range had prostaglandin E levels in the range shown in Table 1. In contrast, as shown in Table 2, excessive synthesis of mediators was seen in 5 eyes with bacterial endophthalmitis or other conditions.

It was not anticipated by the author that the contents of the Arthur (LIM) Lecture would be published, and a very similar paper had already been published in a book edited by Prof. Yuan Jia-Qin. The present paper is thus a slightly modified version of that earlier paper.

Table 3. Types and Characteristics of Pseudophakic Ocular Endophthalmitis from the Viewpoint of Period of Onset and Symptoms

	Fibrin response	Endophthalmitis accompanied by fibrin and vitreous opacity	Toxic lens syndrome	UHG syndrome	Phacoanaphylactic uveitis	Bacterial endophthalmitis (1)	Bacterial endophthalmitis (2)	Bacterial (or fungal) endophthalmitis (3)
Period of onset	4-6 days	2-3 weeks	2-5 days	Late onset, but also occasionally early	After 2 weeks	1-2 days	4-10 days	Usually more than 2 weeks after
Symptoms								
Extraocular stimulation	—	—	—	±	±	+++	++	+
Dolor	—	—	—	+	±	+++	++	+
Anterior chamber inflammation	+	++	++	++	++	+++	++	++
Anterior chamber empyema	—	—	++	—	+	+++	++	+
Fibrin	+	+	+	-	±	+	+	+
Vitreous opacity	—	+	+	+	++	++	+	+
Retinal phlebitis	—	—	—	-	—	++	+	+
Ocular hypertension	—	—	—	++	+	—	—	—
Steroid effect	+++	++	+++	+?	+?	+?	+?	+?
Antibiotic effect	—	—	—	—	—	+++	+++	+++
Notes	Prevented by anti-PG agents	More cases must be gathered to establish clinical entity	Recur	Mostly in anterior chamber	Mutton-fat keratic precipitates	Part of S. aureus and Gram-negative bacterial	Part of S. epidermidis and Gram-positive bacteria	Anaerobe, mycete

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