Summary
Around our fiftieth year, many of us have difficulty seeing objects close up and need reading glasses. The inability to focus at a short distance is referred to as presbyopia. It is caused by loss of accommodative ability.

Accommodation is the change of the optical power of the eye, making it possible to focus up close. What exactly happens during accommodation? Around 1853 (almost at the same time as Anthonie Cramer in Groningen), Berlin physiologist von Helmholtz uncovered the changes occurring inside the eye during accommodation. Accommodation is accompanied by contraction of the ciliary muscle surrounding the lens (Figure 1).

![Diagram of the eye showing changes during accommodation.](image)

**Figure 1.**

The lens is attached to this ciliary muscle via thin zonular fibers. Ciliary muscle contraction causes the suspension points of the zonular fibers to shift inward. As a result, the zonular fibers are pulled less hard and, due to the elasticity of the lens capsule and the lens material, the lens may assume a rounder shape, especially in front. During disaccommodation, the zonular fiber tension increases once more,
flattening the lens back into its original shape. Owing to age-related changes in the
accommodative mechanism, for instance due to the greater stiffness of the lens, lens
defformation is impaired in the long run. One then needs reading glasses to be able to
see up close.

It is obvious at once that it might be a good idea to try and replace the stiff lens
material by a soft, clear material to restore accommodation. This, however,
necessitates eye surgery. Somewhat comparable operations are commonly
performed because of age-related cataract; in which case the patients’ lenses
become clouded with age. During cataract surgery the clouded lens is removed and
replaced by an artificial lens. The optical power of these artificial lenses allows the
patient to focus on distant objects without glasses, since currently available artificial
lenses are unable to provide accommodative ability. Even with an implant, glasses
will therefore be needed for reading. Patients would find it useful if the artificial lens
were not only to restore the vision, but also the ability to focus at several distances.

This thesis concerns the development of an accommodative artificial lens. The
idea is to remove the cloudy lens material through a small incision (1 to 1.5 mm) in
the lens capsule and then to fill the lens capsule with a soft clear material. The
company Pharmacia in Groningen in the Netherlands (manufacturer of artificial
lenses, now operating under the company name AMO Groningen BV due to a take-
over) has developed a silicone-based polymer that may serve as a filling material for
the lens capsule.

A suitable surgical technique had to be developed first in order to be able to
utilize the filling material. In this context, the lens material had to be removed from the
lens capsule and the filling material injected into the lens capsule without risking any
leakage. Thus, a suitable plug was conceived to close the opening in the lens
capsule, keeping the injected material inside. Chapter 2 contains the patent
describing the developed plug. This plug made it possible to fill the lens capsule to a
greater or lesser extent and to study various filling levels.

Chapter 3 describes experiments involving human donor eyes originating from
the cornea bank of the Netherlands Ophthalmological Research Institute. Originally,
these eyes had been stored for corneal transplantation, but were rejected. In 10 older
eyes, the lens was filled with the silicone material and closed with a plug. Then this
lens, together with the zonular fibers and the ciliary muscle, was removed from the
eye and suspended on sutures in a ring. Simulated accommodative changes were
effected by pulling out the ciliary muscle via sutures controlled by a motor. The optical power of the lenses was measured during this simulated accommodation. The optical power changes in the refilled lenses were compared to the changes in non-operated lenses of donor eyes. This revealed that the natural lenses of older donors remain unaffected by tensile forces, while silicone-filled lenses with a comparable age did result in certain variations of the optical power. All of this supports the idea that refilling the human lens capsule may restore accommodation.

The required optical power of the artificial lens for the eye in question is determined prior to performing any eye surgery for lens implantation. Manufacturers of currently available artificial lenses supply their products in increments of half a diopter to a full diopter. In the case of an injectable lens, the surgeon may determine the power of the resulting artificial lens. Chapter 4 investigates whether varying the infusion height used during refilling may influence the power of silicone-filled lenses. These experiments were performed on pigs’ eyes obtained from a butchery. Another parameter to be investigated was the size difference between refilled lenses equipped with a plug (chapter 2) and a group where no such plug was used. It turned out that the infusion height indeed influences the power of the injected lens; although the optical power has a very limited range of variation. Capsular bags sealed off with a plug resulted in lenses with a size and configuration which is comparable to that of natural porcine lenses.

The optical power of a lens which is created by injection of silicone material in the lens capsule, is determined by the amount of injected material. Chapter 5 describes experiments using porcine eyes to elucidate the correlation between the amount of injected silicone material and the optical power of the lens, the correlation to the thickness of the lens and the correlation to accommodative changes due to the tensile forces on the ciliary muscle. The detected correlation between the refill volume and the optical power (0.04 mL/D\(^{-1}\)) provides an indication of the required refilling precision. The detected relation between the lens thickness and the optical power of the lens (0.54 mm/D\(^{-1}\)) may have an impact on the refilling procedure. It may, after all, become clear that the lens thickness may be easier to determine than the optical power of the lens. In a setup where accommodation was simulated by applying tensile forces to the ciliary muscle, it was found that lens capsules filled more to capacity also decreased the accommodative amplitude. This result confirms earlier findings by a different researcher.
Postoperative cataract is a very common occurrence after implantation of artificial lenses. Postoperative cataract may be attributed to the cells that remain on the inside of the lens capsule after removal of the lens material. These lens epithelial cells change their properties after surgery, clouding and shrinking the lens capsule, which impairs the patient's vision again. The treatment of postoperative cataract after implantation of currently available artificial lenses consists of a laser treatment to remove the central part of the clouded lens capsule. Laser treatment, however, is unsuitable for soft injected lenses, since the capsule has to remain intact in order to keep the soft material inside the lens capsule. Chapter 6 describes a number of experiments focusing on the occurrence of postoperative cataract by killing off remaining lens epithelial cells during surgery. Lens cataract surgery currently lasts between five and thirty minutes. We therefore aimed at a treatment focusing on the occurrence of postoperative cataract lasting no more than five minutes. In a laboratory assay, cultured lens epithelial cells were placed in an environment with toxic substances or in an aqueous medium for precisely this length of time. The question was whether the cells would be able to continue growing after this. In a parallel experiment, lenses originating from fresh porcine eyes obtained from butchery were operated on and - after killing off the lens epithelial cells - were filled with silicone material. In the next step, the porcine lenses were placed in an incubator and remained there for a certain period of time, preparatory to counting the lens epithelial cells through a microscope. A five-minute exposure to actinomycine D was effective in killing off cultured lens epithelial cells; besides, in the experiment with the filled porcine lenses, actinomycine D also minimized the number of lens epithelial cells found on the inside of the lens capsule. This demonstrates that actinomycine D is a suitable agent to prevent postoperative cataract.

The natural lens is characterized by a gradient refractive index. The refractive power of this gradient-index lens increases from the periphery of the lens to its center. Removal of the lens material and filling of the lens capsule with silicone material will alter the optical properties of the lens, because the silicone material, on the other hand, has a homogeneous refractive index. Refilling may also influence the lens curvature, thus changing the optical properties. It is not only the power of the resulting lens that is important when refilling the lens capsule, but it is also imperative to make sure that no other optical aberrations occur that may affect the optical quality to an unacceptable degree. Chapter 7 investigates the effect of gradient refractive
index and lens curvature changes. The optical power of the lens and the degree of spherical aberration in porcine lenses were determined before and after refilling, respectively. Spherical aberration is a refractive problem; in this case the light rays refracted by the edge of the lens have a different focal point distance than the light rays at the center. It was found that, in porcine lenses, using a lens with a homogeneous refractive index instead of a gradient-index lens had a major impact on the spherical aberration. It remains to be seen what the consequences are for patients receiving an injectable lens. The size and configuration of a human lens is very different from that of a porcine lens, which is why these results cannot just be extrapolated to human subjects.

Since the accommodative mechanism of rhesus monkeys most strongly resembles that of the human eye, experiments involving adolescent rhesus monkeys were performed. Rhesus monkeys are useful models because, like people, they develop presbyopia at middle age. In each animal, the lens material in one eye was removed and the lens capsule was then filled with the silicone material. A special protocol was used to prevent postoperative inflammatory reactions as well as postoperative cataract. During surgery, the inside of the capsule was, among others, treated with actinomycine D, which, according to Chapter 6, is a valuable agent in preventing postoperative cataract. In order to prevent this toxic substance from escaping from the capsule and damaging other structures in the eye, the actinomycine was dissolved in a viscoelastic material (sodium hyaluronate) which could be selectively introduced into the capsule. After surgery, accommodation was stimulated by local pilocarpine or carbachol application onto the operated eye, causing ciliary muscle contraction. The resulting optical power changes of the eye were then measured. A certain degree of postoperative accommodation was detected. During the 37-week follow-up period, postoperative cataract developed slowly, although the optical power of the operated eyes could be measured during the entire follow-up period.

Conclusion. This dissertation describes a number of preparatory studies concerning a suitable injection material for accommodative artificial lenses. It is hopeful that it was possible to implant such a lens in human donor eyes and that accommodative changes could be measured (Chapter 3). An important aspect is the possibility of actually measuring accommodation in Rhesus monkey eyes with implanted lenses and obtaining the optical power for an extended period of time.
(Chapter 8). The accommodative performance in older (presbyopic) animals remains to be elucidated. Prevention of capsular clouding is a major aspect with regard to the future development of injectable accommodative artificial lenses. Besides, there are other more technical issues to be solved. One of these is the question of how to measure and control the power of the injected lens during surgery. In the context of the experiments described in this dissertation, the natural lens was mostly removed by simple aspiration. Another question is how the hard, stiff natural lens material found in older cataract patients can be removed through a 1 to 1.5 mm opening in the lens capsule. This technique needs to be developed as well.

In view of the considerable interest in presbyopia correction among ophthalmologists, the prospects for further development of accommodative lenses are favorable.