INVESTIGATIONS OF THE REASONS FOR SUCCESS AND FAILURE IN THE ANTERIOR SHUNT-TO-THE-ENCIRCLING-BAND PROCEDURE IN THE TREATMENT OF REFRACTORY GLAUCOMA

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INTRODUCTION

THE ANTERIOR-CHAMBER SHUNT-TO-THE-ENCIRCLING-BAND (ACTSEB) PROCEDURE offers a high degree of success (65% to 96%) even in refractory glaucomas. The aqueous humor is shunted from the anterior chamber through a Silastic tube to a reservoir between the encircling band and the sclera. When the procedure is successful, there is no postoperative conjunctival bleb such as one sees in the standard anterior filtering procedure. If one has the opportunity to examine the Silastic tube, it is seen to be located in the gutter of the encircling No 20 silicone band. The lumen of the tube remains patent despite a well-formed capsule surrounding the silicone band.

It is the purpose of this thesis: (1) To review the history of setons in glaucoma surgery. (2) To demonstrate the fate of the aqueous in the reservoir, using horseradish peroxidase (HRP). (3) To review the chemistry of silicone. (4) To review the role of silicone in the formation of the enveloping fibrous capsule. (5) To present in vitro studies that explore the development of the capsule around silicone implants. (6) To discuss the ACTSEB failures and techniques in order to avoid them. (7) To present a revised ACTSEB device that incorporates the findings of the above studies.

HISTORICAL REVIEW OF SETON FILTERING PROCEDURES

Standard glaucoma procedures afford a high incidence of success in favorable eyes. However, the limited success of these procedure in aphakic neovascular glaucoma and in other refractory glaucomas has prompted surgeons to insert setons for the relief of intraocular pressure (IOP).

Although there have been sporadic reports of seton surgery since ancient times, the earliest documented procedures were performed by Rollet and Moreau[1] in 1906. The wide variety of seton operations can be conveniently reviewed on the basis of the anatomic area into which aqueous humor is drained.

AQUEOUS HUMOR SHUNTED TO THE SUBCONJUNCTIVAL SPACE

Limbal Region

In 1906, Rollet and Moreau[1] used horsehair threaded through a double paracentesis wound in the inferior cornea to treat 18 cases of corneal ulcer complicated by hypopyon. Since this procedure might prove effective in treating cases of inflammatory glaucoma, Rollet[2] used it in two patients with absolute glaucoma the following year. Satisfactory results were achieved.

In 1912, Zorab[3] used a silk thread as a wick to drain fluid from the anterior chamber to the subconjunctival space, a procedure known as the needle operation. He passed a silk suture under the conjunctiva, through the limbal area, and across the anterior chamber to emerge in the subconjunctival space on the opposite side. Since he had difficulty in passing this suture through the limbal area, he devised a procedure which he termed "aqueoplasty."[4] He raised a conjunctival limbal-based flap from the 10:30 o'clock to the 1:30 o'clock position and made a keratome incision at the 12 o'clock position. A bend of silk was then placed in the chamber anterior to the iris, and the distal suture ends were allowed to lie on the exposed sclera. The conjunctiva was then closed with two sutures. Zorab[4] reported the results of the needle operation in 6 eyes and of the aqueoplasty in 15 eyes. Ocular tension was determined by touch. Following the needle operation, the tension was normal in one eye for 4 months; in one eye the suture was observed in the subconjunctival area near the limbus, and Zorab therefore presumed that the needle had not entered the anterior chamber. In four eyes, the suture was removed because of exposure. The aqueoplasty technique was used to normalize the tension in nine eyes for periods of 1 to 9 months but failed to lower the pressure in one eye. Complications of the aqueoplasty technique included loss of the eye, resulting from endophthalmitis, and exposure of the suture in four eyes. Zorab considered a scarred conjunctiva to be a definite contraindication to the operation.

Wood,[5] in 1915, presented to the Chicago Ophthalmological Society two cases of glaucoma in which he performed aqueoplasty with normalization of the tension (3-month follow-up). He cleverly modified the aqueoplasty operation by placing the suture into the anterior chamber,

using a Graefe knife with a hole near its point.[6] The knife transfixed the cornea through the limbal area at the 11 o'clock and 1 o'clock positions, creating two openings into the anterior chamber. The suture was threaded through the hole in the tip of the knife, and the knife was then withdrawn, leaving a suture in the anterior chamber. The free ends were theaded on needles and positioned subconjunctivally. This operation was successful in normalizing the tension in one eye with secondary traumatic glaucoma (1-month follow-up) and in a second eye with congenital glaucoma (3-month follow-up).

Stefansson[7] placed a T-shaped device of 22-carat gold in the anterior chamber through a keratome incision at the 12 o'clock position. The vertical part of the T was placed in the anterior chamber, and the two limbs on the sclera were covered by conjunctiva. He reported pressure control in 78% of 32 eyes, which were followed for an average of 3 years. Complications included perforation of the conjunctiva by the gold wire (two cases), implant dislocation (one case), and iris atrophy where the gold contacted the iris in a few cases.

Gibson,[8] in 1944, attempted to use autologous canaliculus as a seton material for draining aqueous to the subconjunctival space. Using dogs, he sutured the canaliculus into the anterior chamber through a limbal wound and placed the posterior end approximately 4 to 5 mm posterior to the limbus. The lumen of the canaliculus was packed with catgut strands. Histologic study showed the canaliculus graft to be viable, and, in a few instances, there were suggestions of a patent connection between the anterior chamber and the canaliculus. The posterior end of the canaliculus was occluded in every case, and Gibson could not raise a subconjunctival bleb with intracameral saline injection. He reported performing the procedure in one advanced light-perception glaucomatous eye. He inserted the patient's upper canaliculus through an anterior limbal punch wound. The postoperative course was complicated by hypopyon, uveitis, superior lens opacity, and scarring of the subconjunctival opening of the canaliculus. The IOP rose to the preoperative level after 6 weeks.

Bock,[9] impressed by the tolerance of the eye to an intraocular glass foreign body, reported in 1950 the use of rods of glass (Jena or Pyrex) to relieve glaucoma in rabbit eyes. In two eyes, the canal formed by the tube was lined by endothelium. Removal of the tube 10 days prior to enucleation resulted in closure of the canal by dense connective tissue. Bock overcame the problem of rod slippage, either intracamerally or subconjunctivally, by enlarging and flattening both ends of the rod. He reported short-term success with this device in two patients.

Muldoon et al[10] chose platinum as a seton; the element would give no

electrolytic reaction and therefore no inflammatory response. However, when platinum wire was implanted in the anterior chamber of the rabbit eye, a transient exudate formed around the wire in one eye and adhered to the iris and lens in others. Muldoon and associates[10] used plantinum wire as a seton in glaucoma surgery performed on two patients. In one case, a flat coil of four loops of platinum wire was placed into the anterior chamber after a keratome incision, and the ends were buried beneath a fornix-based flap. An aqueoplasty-style procedure using four loops of platinum wire was performed on a second patient. Both operations resulted in a functioning bleb with control of IOP over a 2-year follow-up period.

Qadeer,[11] impressed with the tolerance of the Ridley acrylic lenses in cataract surgery, used polymethylmethacrylate sheeting to cut a 4 × 6-mm rectangular implant with a 2-mm round head. The head was inserted into the anterior chamber under a limbal-based flap following a peripheral iridectomy. The implant was secured to the conjunctival flap with sutures. Fourteen eyes were treated; 2 were followed for 6 months, and 6 were followed for 3 months. Two cases required revision with replacement of a second plate. Qadeer cited two possible complications: slipping of the plate into the anterior chamber and slipping of the head out of the anterior chamber. All patients were found to have normal tension at the postoperative follow-up.

Laval[12] used absorbable gelatin film (Gelfilm) of 0.075-mm thickness as an adjunct to iridencleisis surgery. He found little inflammation and no giant-cell formation or fibrous proliferation surrounding sheets of Gelfilm extending from the anterior chamber to the subconjunctival area. He performed one pillar iridencleisis on 24 patients; the prolapsed pillar was covered by a 4 × 10-mm sheet of Gelfilm. The tension was found to be normal postoperatively in all cases (follow-up between 2 weeks and 12 months).

Lehman and McCaslin[13] noted a similar noninflammatory reaction to Gelfilm setons in rabbits. These investigators placed a strip of Gelfilm under a limbal-based flap from the anterior chamber to overlie the sclera in two eyes. In both eyes, a plastic iritis ensued. Removal of the Gelfilm 2 weeks after surgery resulted in an abatement of the inflammation.

Troncoso,[14] impressed with the excellent results obtained by the neurosurgical use of tantalum plates in the repair of cranial defects, explored the tolerance of the rabbit eye to tantalum wire. He placed the wire in the ciliioscleral sinus; the tips of the wire appeared in the anterior chamber. The cornea in front of the implant became opaque 2 days after the operation and 1 week later vascularized. Exudates formed on the poste-

rior surface of the cornea where it was in contact with the metal. Troncoso also attempted to keep a limbal trephine hole open by suturing tantalum wire to the sclera and uniting the ends in a tufted, twisted configuration that elevated the conjunctiva from the sclera. In some cases, the trephine holes closed with fibrous tissue in 4 to 6 weeks, while in others the opening remained patent for 2 to 8 months. A tantalum tube placed in a trephine hole became displaced into the vitreous, and the hole became closed with fibrous tissue.

MacDonald and Pierce[15] used silicone strips as setons in rabbit eyes. The strips spanned the superior part of the anterior chamber, and the free ends were buried under the conjunctiva or exteriorized in the limbal area. Almost all of these seton drainage operations failed within 2 months. In one experiment, however, subconjunctival drainage persisted for 8 months. The authors did not place their setons in human beings.

Posterior Region

Many setons designed to drain aqueous to the limbal area are prone to dislocate or erode through the conjunctiva. This has provided impetus to design seton devices that are better fixed to the ocular wall. Such fixation can be achieved by inserting the seton in cyclodialysis tracts.

Row,[16] in 1934, placed platinum-iridium wire and horsehair in rabbit eyes. He later implanted horsehair in three human eyes to relieve glaucoma. Complications included hemorrhage from the iris, epiphora, and conjunctival erosion. Row controlled the tension in all three eyes.

Troncoso,[17] in 1940, used magnesium as a seton both experimentally (with rabbits) and clinically. He found that a 1-mg piece of magnesium placed in the anterior chamber or in the vitreous of the rabbit eye dissolved and caused minimal inflammation. He inserted a 2 × 8-mm long strip in a cyclodialysis cleft and bent the external tip 5 mm vertically to allow the excess of hydrogen bubbles from the dissolving magnesium to escape subconjunctivally under the fornix-based flap. Bubbles filled the anterior chamber in a few days, and inflammatory signs subsided 2 to 3 weeks after the operation. The tension in the surgically treated eye remained lower than in the control. Histologic sections did not reveal a clear channel from the anterior chamber to the suprachoroidal spaces; the channel was either filled with connective tissue or contained cystic spaces lined with connective tissue. Troncoso performed 12 similar operations on human beings, with good results in two eyes, partial success in four, and failure in four. Complications included vitreous loss, detachment of Descemet's membrane, hyphema, and inflammation.

In 1949, Bick[18] tried to keep the cyclodialysis cleft open with tantalum wire and tantalum plates. Because he noted episcleral-tissue downgrowth

into the cyclodialysis tract in experimental animals (rabbits), in clinical use he buried the tantalum in the suprachoroidal space instead of externalizing it in the subconjunctival space. In all four human cases of glaucoma treated in this manner, the pressure was controlled for up to 2 weeks and then returned to the preoperative elevated values.

Bietti,[19] in 1955, buried polyethylene plates in the cyclodialysis clefts of eight glaucoma patients. The IOP was controlled in five patients. Length of follow-up was not mentioned. He also normalized IOP in two glaucoma patients, using a polyethylene tube that extended from the anterior chamber, through the cleft, and into the subconjunctival space. Length of follow-up was not mentioned.

In 1958, Barsky and Schimek[20] used gelatin film as an adjunct to the cyclodialysis operation. Since Gelfilm is nonantigenic, the authors predicted that it would be completely absorbed (leaving a patent cleft) and no inflammatory host response. They inserted gelatin film in the anterior chambers of 15 rabbits. In three rabbits, the cleft remained patent but was lined by fibrous tissue. In 12 rabbits, the cleft was closed by considerable chronic inflammation produced by the Gelfilm. Because of these poor results, the authors did not recommend a clinical trial.

Ellis,[21] in 1960, attempted to stabilize a silicone-rubber seton connecting the anterior chamber to the subconjunctival space. The anterior and lateral walls of the tube were removed so that a previously fashioned pedicle scleral flap could bridge the gap and stabilize the seton. In 20 of the 40 rabbits, the tube slipped either posteriorly or into the anterior chamber, thus rendering this type of implant undesirable.

La Rocca,[22] devised a U-shaped polyvinyl tube with 8-mm tubes and a 2-mm bridge. After creating a fornix-based flap, he inserted each tube in a cyclodialysis cleft 6 mm from the limbus so as to project approximately 2 mm into the anterior chamber. La Rocca named this procedure gonioplasty.

Gills et al[23] used a Teflon tube in performing gonioplasty on a glaucomatous eye in which intraocular manometric measurements were made both before and after surgery. The lowered IOP was the result of both a decrease in aqueous formation and a marked increase in aqueous outflow.

Richards and Van Bijsterveld[24] modified the La Rocca technique by securing the bridge of the U-shaped tube with a scleral flap. This was used in nine eyes of eight patients. Two eyes did not have controlled IOP postoperatively, but the remaining seven eyes had well-controlled pressure without medication for a follow-up period of 8 to 14 months, despite the absence of a functioning bleb and despite decreased outflow. The authors postulated that control of IOP postoperatively was due to de-

creased aqueous production from a localized and permanent displacement of the ciliary body. In a long-term study of these patients, Richards[25] noted that in only one of nine eyes was the pressure controlled without medication. In an eye enucleated 5 years after gonioplasty because of absolute glaucoma, there was no evidence of degeneration of the cornea, sclera, or ciliary body in the vicinity of the seton.

Blumenthal et al,[26] using rabbits, inserted tubes fashioned from autogenous rib cartilage; they predicted that the cartilage seton would be well tolerated and integrated into surrounding tissues without the problems of rejection and slippage. An autogenous cartilage tube (3 to 6 mm in length, with external diameter of 1.5 mm and internal diameter of 1 mm) was inserted into the anterior chamber through a limbal incision under a limbus-based conjunctival flap; there was no tube fixation. Of 57 eyes, bleb failure occurred in 22 within 7 to 48 days postoperatively. On histologic study, this failure was seen to result from connective-tissue invasion of the tube. In the 33 eyes with functioning blebs, an endothelial-like tissue lined the inner surface of the tubes. Clinically, most eyes showed mild, transient, inflammatory reactions at the site of the implant; these usually resolved within 1 week. The authors predicted that the patent tubes would also eventually close by invasion of subconjunctival connective tissue.

Portney[27] tried to enhance the effectiveness of the cyclodialysis procedure by passing the long arm of a T-shaped silicone elastomer sheet through a cyclodialysis cleft and out of a limbal incision. The long end was pulled until the short arms of the T were positioned at the cyclodialysis opening, 6 mm from the limbus. The anterior end of the seton was then folded back and sutured to the T-bar end. This device was used to correct severe secondary glaucoma in five eyes of four patients. The IOP was reduced for 1 month in only one eye that also underwent cyclodialysis. In the three enucleated eyes, an inflammatory reaction obliterated the connection between the anterior chamber and the suprachoroidal space.

Honrubia et al[28,29] inserted a silicone tube through a trabeculectomy under a 3 × 5-mm scleral flap. The tube was secured to the sclera by a suture around the tube. The procedure was performed on 59 eyes having severe neovascular glaucoma. The mean IOP preoperatively was 57 ± 8.7 mm Hg and postoperatively was 27 ± 16.5 mm Hg. Adequate control of IOP (24 mm Hg) was obtained in 37 eyes (63%). Twenty-one eyes required medications to control IOP adequately.

Complications included tube exposure after scleral flap and conjunctival erosion (nine eyes), flat chamber in all eyes during the first 2 weeks, and severe glaucoma or phthisis bulbi resulting in enucleation (four eyes).

Kuljaca et al[30] placed an 8-mm Teflon tube into the anterior chamber of 12 eyes with neovascular glaucoma. The tube was inserted through a limbal incision under a scleral flap after a fornix-based flap was raised. The tube was split 3 mm from the end so that the arms would be well secured to the sclera. In two eyes, the procedure failed because of prolonged flat chamber (4 and 5 months) and exposure of the tube; in another eye, failure was due to hyphema blocking the tube. The remaining nine cases were well controlled for a follow-up of 2 to 24 months.

Krupin et al[31] were concerned that the hypotony seen after filtering surgery might result in scarring of the sclerotomy site and contribute to the formation of cataracts. These authors used a unidirectional-valve device to prevent hypotony following seton-filtering surgery. The valve implant consisted of a 1.5-mm Supramid tube with a beveled end that was joined to a Silastic tube. The end of the Silastic tube was sealed except for horizontal and vertical slits that functioned as a unidirectional valve. The Supramid portion was inserted into the anterior chamber via a keratome incision under the limbus-based flap, and the Silastic end was buried under a limbus-based scleral flap. The two horizontal Supramid sidearms were sutured to the sclera at the anterior-chamber entry site to prevent posterior migration of the implant.

The procedure was performed successfully in two eyes with open-angle glaucoma and one eye with secondary glaucoma. Follow-up ranged from the immediate postoperative period to 3 months and 6 months.

The implant was modified for use in cases of neovascular glaucoma by creating a 160° angle between the Supramid and Silastic portions of the implant to avoid corneal and iris touch.[32] The procedure was modified by performing an iridectomy only when the iris prolapsed into the wound. Iridectomy, in a series of 42 eyes with neovascular glaucoma, caused such diffuse bleeding that the procedure was aborted in 2 eyes. In 40 eyes, a 68% rate of control of IOP at $\leq$ 24 mm Hg was maintained for an average of 13.8 $\pm$ 9 months.

In 1983, Krupin et al[33] reported the long-term results of the Krupin-Denver valve in 79 eyes with neovascular glaucoma followed for a mean period of 23.7 $\pm$ 10.9 months. Twenty-seven eyes required no medications postoperatively; 53 had IOP $\leq$ 24 mm Hg. The procedure failed to control IOP in 26 eyes because of external bleb scarring in 18 eyes and internal closure in 5 eyes. Bleb revision, with excision of subconjunctival and subscleral fibrous tissue, was successful in 10 of 18 bleb failures. The laser was used successfully to treat pupillary-block glaucoma in two eyes and fibrovascular anterior-chamber tube closure in five eyes. Hyphema occurred in six eyes and required irrigation in two eyes. Flat chamber was

seen in one eye. Cataracts were successfully removed in three eyes with functioning valve implants.

Folberg et al,[34] in 1982, described the histologic findings in an eye enucleated following failure to control neovascular glaucoma with a Krupin-Denver valve and cyclocryotherapy. The inner wall of the bleb was infiltrated by large numbers of lymphocytes. A fibrovascular membrane originated from the inner wall of the bleb and progressed over the anterior edge of the value and over the anterior lens surface. A plug of fibrovascular tissue was seen in the mouth of the valve. An intense local foreign-body giant-cell reaction was present around the Supramid portion of the valve.

Vail,[35] in 1907, treated a 75-year-old patient who had absolute glaucoma by passing a black silk suture through the ora serrata, into the vitreous, and out through the sera 8 mm from the entry site. The suture was cut and tucked in the subconjunctival space. The pressure remained normal for 3 months, when the suture was withdrawn, and remained normal until the patient's 24 months after surgery. Presumably, the suture tract created a fistula between the vitreous and sub-Tenon's or subconjunctival drainage since the former drains into a large reservoir, and there is less risk of endophthalmitis from conjunctivitis.

Weekers,[36] in 1922, described the placement of a hollow gold cuff 2 mm and 1.5 mm in height in a scleral trephine hole 7 mm posterior to the limbus. The operation was performed successfully in three cases of absolute glaucoma.

AQUEOUS HUMOR SHUNTED TO THE ORBIT

In 1969, Molteno[37] and Molteno et al[38] described the use of an acrylic implant for the correction of refractory glaucomas. The 8-mm diameter acrylic plate, with a perpendicular 1-mm tube opening onto its anterior surface, was anchored to the postequatorial sclera with sutures, and the anterior tube was inserted through a trephine hole into the anterior chamber. Using local (and sometimes systemic) corticosteroids, excellent short-term IOP control was achieved. There were significant complications, such as bleb perforation and dellen, which were attributed to the presence of such a large implant adjacent to the limbus.

In 1977, Molteno et al[38] used the implant to manage severe neovascular glaucoma in 12 patients. The silicone tube was lengthened to 16 mm to allow the acrylic plate to be placed more posteriorly on the sclera. Follow-up varied from 6 to 38 months. Intraocular pressure in two eyes was controlled without medication, in five eyes was $\leq$ 20 mm Hg, and in four eyes ranged up to 30 mm Hg. Complications included hyphema (12 eyes),

iris blocking the tube (3 eyes), vitreous hemorrhage, and implant exposure (1 eye).

In 1979, Molteno[39] decided that the postoperative hypotony seen during the first 10 days after seton insertion contributes significantly to choroidal detachment and to intraretinal and vitreal hemorrhage, especially in eyes that have had previous surgery, extensive disease, or both. To prevent hypotony, the procedure was divided into two stages. In the first stage, the implant was secured to the globe without connecting the tube to the anterior chamber. Eight weeks were allowed for the plate to be encapsulated by fibrous tissue. In the second stage, the tube was inserted into the anterior chamber, and postoperative hypotony was reduced to less than 24 hours.

To prevent heavy fibrotic encapsulation of the plate, patients were placed on a variable antifibrosis regimen with local and systemic corticosteroids, fluphenamic acid, and colchicine tablets. The two-stage technique reduced the amount of medication needed to control bleb fibrosis. Results were 22 eyes with an IOP of 20 mm Hg, 10 eyes controlled with medication, and 2 eyes with uncontrolled IOP. Complications included tube exposure, transient hyphema, flat chamber, and bleb fibrosis.

In 1981, Molteno[40] tested a modification of the long-tube implant, using the two-stage technique. To enlarge the surface area for drainage, two- and four-plate devices were fashioned with interconnecting spillover silicone tubes. Thus, the drainage surface area was effectively increased from 135 mm^2 in a single-plate implant to 540 mm^2 in a four-plate implant. When implanted in a series of eyes with secondary glaucoma, the two-plate implant offered a significant improvement in IOP control (mean, 12.75 mm Hg) over that of a single plate (mean, 25 mm Hg). A four-plate device caused extended hypotony, and final IOP (mean, 10.6 mm Hg) was similar to the two-plate design. Follow-up ranged from 6 months to 3 years. Molteno[41] did not consider administration of antifibrosis medication to be necessary in patients aged less than 18 months or more than 60 years if glaucoma were not terminal and the eye not congested.

Cairns[42] used the Molteno long-tube implant without the systemic antifibrosis regimen and obtained good results. He noted that the anterior chamber remained flat for 7 to 8 days before reforming.

Brown and Cairns[43] used the Molteno implant in the treatment of 16 cases of neovascular and 14 cases of nonneovascular glaucoma. They were able to control IOP (25 mm Hg) without medications in 17 cases (56%) and with medications in 2 cases (7%); 11 cases (37%) were failures. They limited the use of the antifibrosis regimen to the younger, healthier

patients but found the success rate higher (11 cases or 37%) in the nonregimen group than in the group (8 cases of 27%) successfully receiving the regimen. Results in the diabetic neovascular group were greater (89%) than in the group with neovascular glaucoma secondary to venous thrombosis (57%). Brown and Cairns performed the Molteno operation in a single stage, fearing greater ocular damage by the delay in the two-stage procedure. Complications in the first week included flat anterior chamber (seven cases, one of which ultimately failed) and hyphema (seven cases, three of which ultimately failed). Long-term complications included transient elevated pressure (11 cases, 5 of which ultimately failed).

Peyman et al,[44] in 1974, described a prototype valve unit that would function at an IOP of 18 to 20 mm Hg. The device consisted of a 30-gauge needle with a latex balloon cemented to the hub. The balloon was encased in plastic, except at the end opposite the needle hub. Pig eyes were perfused in vitro using a constant-pressure perfusion device, and the average outflow decreased with increasing perfusion pressures. When the needle was inserted into the anterior chamber, drainage through the balloon slit allowed an average increase in flow ranging from 89.7% at 22 mm Hg to +247.8% at 45 mm Hg. The authors predicted that if the device were to be used in vivo, aqueous would drain into the retrobulbar space, thus eliminating the problem of bleb fibrosis as a cause of shunt failure in anterior subconjunctival or sub-Tenon's drainage systems.

White,[45] in 1985, designed a pump which, when triggered by natural blinking of the eye or digital massage, actively pumps aqueous into and out of a 16- to 18-μl balloon. A 0.60-mm silicone tube is inserted into the anterior chamber under a scleral flap. The flange of the reservoir base plate is secured to the sclera in the equatorial area but not under the rectus muscles. The reservoir-outlet tube is positioned in the retrobulbar space.

Schocket et al,[46] in 1982, devised a technique of shunting aqueous to the orbital space, a process entitled "anterior-chamber tube shunt to an encircling band" (ACTSEB). A silicone tube was inserted into the anterior chamber through a limbal incision under a scleral flap. The tube was secured posteriorly into the groove of an encircling band of No 20 silicone, which was placed equatorially 360° around the globe with grooved side toward the sclera. It was postulated that aqueous would flow into the gutter of the silicone tube and into the space between the capsule and the band and would then permeate the capsule and be reabsorbed by orbital vessels. The procedure was conducted in 19 eyes with severe neovascular glaucoma. After surgery, IOP in 18 of the 19 eyes (95%), followed for periods ranging from 5 to 26 months, was controlled at an average of 16.2

mm Hg compared to the average preoperative IOP at 54.1 mm Hg. Postoperative complications included hyphema (21%), prolonged flat chamber (74%), and acceleration of cataract formation (25%).

In 1985, Schocket et al[47] presented a long-term follow-up of 30 eyes with severe neovascular glaucoma. The IOP was reduced from an average preoperative value of 57.1 mm Hg to 15.8 mm Hg (P 0.001), with an average follow-up of 25 months. Use of a 25-gauge needle to enter the anterior chamber reduced the occurrence and severity of postoperative flat chamber. Other early complications included tube block in the anterior chamber by clotted blood (two eyes) and fibrinous iritis (one eye). Late complications included cataract progression and pupillary-block glaucoma. Surgical revision was successful in relieving a tube blocked by iris or blood in the anterior chamber, and laser iridectomy was used successfully in the eye with pupillary-block glaucoma. A progressive corneal opacification in one eye, resulting from tube touch, necessitated tube replacement and repositioning. The shunt procedure was also successful in four of five complicated non-neovascular aphakic glaucomas.

Sarkies and Hitchings[48] used the technique of the anterior-chamber shunt to an encircling band in 20 cases of refractory glaucoma followed from 6 to 15 months. In 9 out of 20 eyes, IOP has remained below 25 mm Hg without medications, and 4 eyes have been controlled (25 mm Hg) with the use of timolol maleate. Complications included tube exposure (two eyes) and blockage of the tube (four eyes). The tube blockage has been revised, and pressure has remained controlled.

In a written communication, Joseph and colleagues reported the design of a silicone tube attached to a silicone band 9 to 12 mm in width. A slit in the tube at the junction with the band provides a pressure-gradient limiting valve. The tube is inserted into the anterior chamber at the limbus or through a cyclodialysis cleft. The aqueous is postulated to exit through the slit valve in the tube on the surface of the encircling band and into the surrounding space between the capsule and the band. The band is attached to the globe by sutures through the anterior edge. This device, therefore, combines the anterior surface drainage onto an implant of the Molteno device and the encircling band of Schocket. The device was inserted in 19 eyes, including six failures of a Schocket-style procedure. All 19 eyes had IOP below 18 mm Hg at 9 months postoperatively. Complications included transient pressure rise 1 month postoperatively, corneal edema, tube-endothelial touch, and band exposure.

Shunts to Veins

Lee et al,[49] in 1968, shunted aqueous through a polyethylene tube from the anterior chamber to a vein on the anterior surface of the superior

rectus in seven normal macaque monkeys. Histologic studies on five eyes were performed between 6 weeks and 12 months following surgery. Prior to enucleation, five eyes were dissected in vivo. The shunt was found to be patent in three eyes and closed in two. One of the closed shunts had migrated into the anterior chamber; the other had perforated the venous wall. Although a hyphema was not clinically noted on histologic section, red blood cells were seen trapped in the trabecular meshwork, Schlemm's canal, and collector channels. The histologic studies showed no evidence of connective-tissue ingrowth in the tubes. Two monkeys with a patent shunt 6 to 9 months after surgery were placed in an upside-down position for 15 minutes prior to dissection in an attempt to induce venous backflow in the anterior chamber. In the five eyes with patent shunts, IOP was lowered by 20% to 25% of the original value, and aqueous outflow was increased.

The authors concluded that the gradual and spontaneous hardening of the polyethylene tube after surgery was an important factor in the failure of the aqueous-venous shunt.

Lee and Ward[50] reported long-term results of anterior-chamber to vortex-vein shunts on 16 eyes. Collagen tubing was used in 14 eyes, while a silicone polycarbonate-block copolymer tubing was used in 2 eyes. Twelve of 16 eyes (75%) benefited from the procedures. The average reduction of IOP was 25% to 50% of the preoperative value. In all 16 eyes, the mean IOP was 30.4 ± 8.5 mm Hg before the operation and 18 ± 7.6 mm Hg after the operation. In three eyes, despite a doubling of outflow, postoperative IOP gradually returned to the preoperative level and required antiglaucomatous medication. Flat anterior chambers were noted in four eyes, which required surgical intervention Gonioscopy showed the tubing to be located anterior to Schwalbe's lines. Failures occurred in four eyes because of adhesion between the cornea and tubing (three eyes) and adhesions between the iris and tubing (one eye). In one case, a portion of the anterior end of the tubing fell into the anterior chamber when the extraocular part of the collagen was absorbed.

The authors attributed the failure, in cases where the tubing was patent and intact in the anterior chamber, to either an early absorption of the extraocular portion of the collagen tubing or blockage of the distal end of the tubing by a thrombotic or inflammatory process.

THE FUNCTIONAL BASIS OF THE ACTSEB PROCEDURE

DETECTION OF ORBITAL FILTRATION IN RABBIT EYES TREATED WITH THE ACTSEB PROCEDURE

Horseradish-Peroxidase Studies

The ACTSEB procedure results in the formation of a fibrous capsule over the encircling No 20S implant; aqueous fluid draining through the Silastic tube in the anterior chamber is known to flow into and expand this capsule.[46,47] More obscure, however, has been the route of filtration of the aqueous out of the capsule and into the orbit.

HRP is a histologic stain that is particularly useful in the demonstration of the permeability of biological membranes.[51] It has been used to study flow within the kidney nephron[52] and, more recently, as a tool for the study of the neuroendocrine cell and the blood-brain barrier.[53]

In this study, HRP is ued to determine the fate of aqueous in the capsule reservoir of eyes treated with the ACTSEB procedure.

Materials and Methods

Six 2-kg New Zealand albino rabbits, on which the ACTSEB procedure has been performed in one eye 3 months previously were anesthetized with ketamine hydrochloride (100 mg/kg) and acepromazine maleate (2 mg/kg of body weight). Using a 30-gauge needle and two 1-ml syringes coupled through a two-way stopcock, 200 μl of aqueous fluid were drained from the anterior chamber of one eye and immediately replaced with an equal volume of 3.4% type VI HRP. This procedure was then repeated in the rabbit's second eye.

After 30 minutes, the anesthetized rabbit was positioned chest upward; following the methodology of Broadwell and Brightman,[53] a 12-cm longitudinal incision was made over the sternum, and the ribs were retracted exposing the heart. A 1-cm incision was made in the right atrium, and 500 ml of normal saline were rapidly infused into the left ventricle through a 13-gauge needle. Exsanguination was considered sufficient when blood draining from the right atrium began to clear. The descending aorta was quickly clamped with a hemostat, and the perfusing-fixation solution (2% glutaraldehyde, 2% formaldehyde, and 0.025% $CaCl_2$ in 0.1 M sodium cacodylate buffer, pH 7.4) (modified Karnovsky's fixative) was rapidly infused. Approximately 1 l of the perfusate was infused over 5 to 10 minutes. Adequate in situ fixation was clearly evidenced by animal tissue becoming hard to the touch throughout the perfused cephalad circulation and soft throughout the unperfused caudad circulation.

Both the ACTSEB and the opposite untreated (control) eye and orbit

were carefully exenterated, sagitally bisected, and immediately transferred to pure sodium cacodylate buffer. Following two washes in the buffer, the eyes with intact orbit were cut into sections 5 mm thick, incubated in 1% osmium tetroxide for 2 hours, and washed again in the cacodylate buffer. Representative sections of 1 × 3 mm were then taken from areas of interest in both the control and experimental eyes and were dehydrated by incubation in an ascending series of methanol concentrations. Dehydration was followed by incubation in pure propylene oxide and, in an ascending series of Epon cncentrations, in propylene oxide. The final Epon incubation was followed by curing for 48 hours in a 60°C oven. Finally, the embedded sections were mounted on blocks and submitted for microsectioning (Sorvall) and subsequent examination with transmission electron microsurgery (Phillips 201C).

For examination of the peroxidase-stained sections with light microscopy, processing was exactly as described previously until the osmium tetroxide step. This step was omitted, and the tissue was incubated either in Goodpasture's nitroprusside-benzidine peroxidase (which stains peroxidase dark blue[51]) or in 3,3'-diaminobenzidine (which stains the peroxidase granules brown[52]). Stained sections were mounted on glass slides for examination under light microscopy.

Results

Gross Sections.—Fig 1A shows the sagitally bisected, exenterated ACTSEB specimen following injection of HRP into the anterior chamber and diaminobenzidine incubation. The Silastic anterior-chamber tube was slightly dislocated by the sectioning of the tissue. The cornea, iris, and conjunctiva demonstrated minimal evidence of HRP reaction product. Overlying the region of encircling silicone band (arrow) at a position approximately 12 mm from the limbus, the orbital tissue began showing an extremely dense reaction product that extended to the orbital apex (Fig 1B). The control specimen (Fig 1C) revealed minimal reaction product (arrow).

Light Microscopy.—The low-power view shows an HRP reaction (large arrow) in the cavity between the silicone encircling band (displaced on processing) and its surrounding capsule (Fig 1D). The reaction product is seen staining the lamella of the capsule.

The high-power view shows an HRP-reaction product diffused throughout the orbital tissues (Fig 1E). The heaviest concentration is found surrounding the blood vessels and within the walls of the vessels (arrow).

Electron Microscopy.—The HRP reaction product is seen lining a space

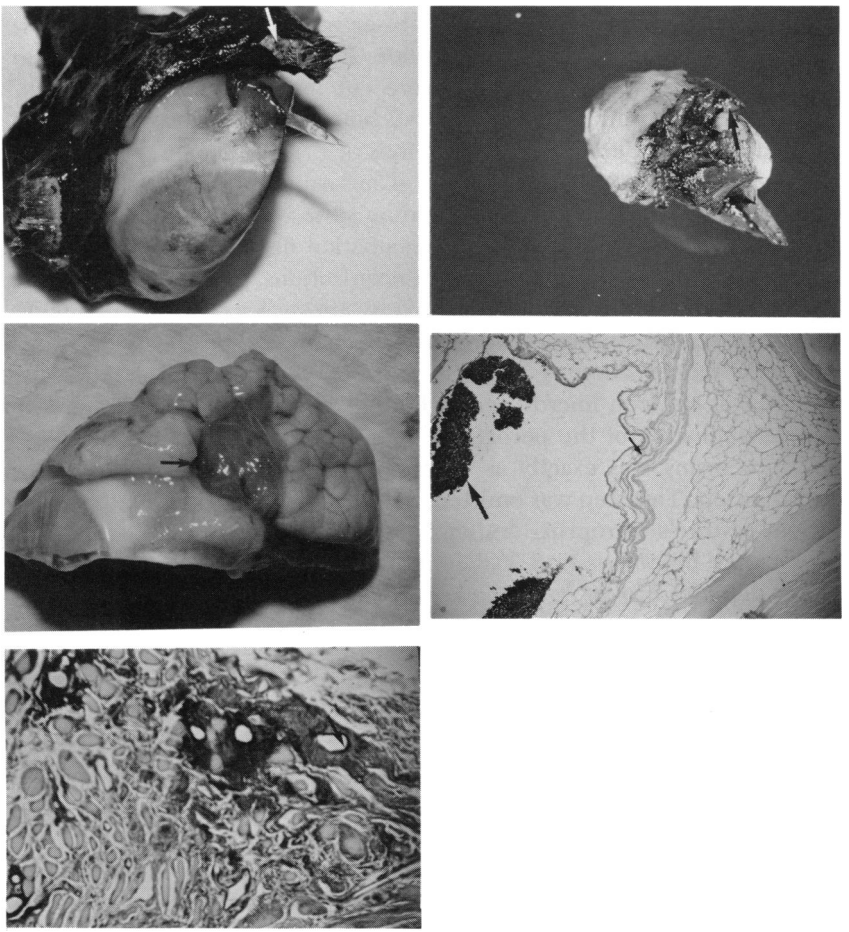


FIGURE 1

A: Sagittal hemisection of exenterated specimen of ACTSEB rabbit eye following HRP injection into anterior chamber and incubation in 3,3′-diaminobenzidine. This view shows minimal reaction product in anterior segment, with dense reaction product extending from area of encircling band (*arrow*) posteriorly. B: Sagittal view of an ACTSEB eye following HRP injection into anterior chamber and incubation in 3,3′-diaminobenzidine. This view shows reaction product extending from orbital tissues overlying encircling band (*arrow*) posteriorly. C: Sagittal hemisection of exenterated specimen of control rabbit eye following HRP injection into anterior chamber and incubation in 3,3′-diaminobenzidine. Section shows minimal reaction product (*arrow*). D: Reaction product is seen in lamella of capsule (*small arrow*) which surrounds displaced silicone band. A heavy concentration of reaction product (*large arrow*) is seen in this space (× 80). E: HRP reaction product concentrates around and within blood vessel walls (*arrows*) (× 200).

between collagen bundles (Fig 2A, black arrows) and on the surface (open arrows) of a cross section of collagen bundles (white arrow). On a higher magnification (Fig 2B), the endothelium (thin arrow) of a vessel is clearly visible. Granules of HPR-reaction product (open arrow) are visible within the endothelium. The HRP-reaction product is also seen in the vessel lumen (asterisk) and coating a red blood cell (thick arrow).

Contrast-Enhanced Computed Tomography Studies

Materials and Methods.—A 3.5-kg New Zealand male Albino rabbit that had received bilateral ACTSEB implants 5 months previously was sedated with ketamine hydrochloride (100 mg/kg) and acepromazine (2 mg/kg body weight). A baseline coronal-section computed tomography (CT) scan study was performed. The anterior chamber of the left eye was perforated with a 25-gauge needle attached to a two-way stopcock to which were attached two Hamilton syringes, one empty and the other containing meglumine diatrizoate (Angiovist), a radiopaque dye.

After 200 μl of aqueous was withdrawn, 200 μl of the dye was injected into the anterior chamber.

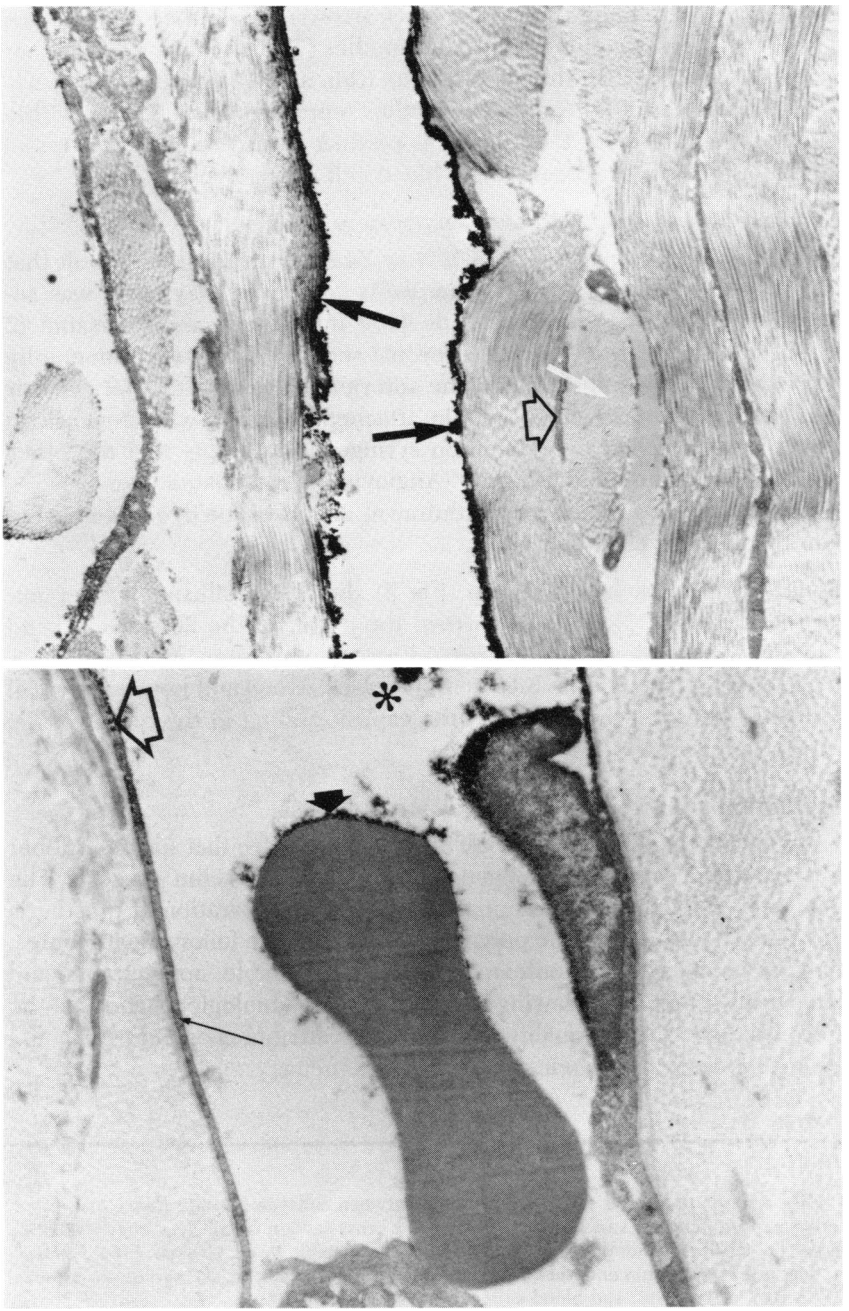
Results.—The baseline CT scan (Fig 3) shows the silicone-rubber implants bilaterally. Note (white arrow) the gutter of the 20 silicone band apposed to the sclera (white arrow). Five minutes after injection, dye is seen coursing through the Silastic tube (black arrow) and beginning to fill the space between the band and the capsule, filling in the gutter of the band (white arrow).

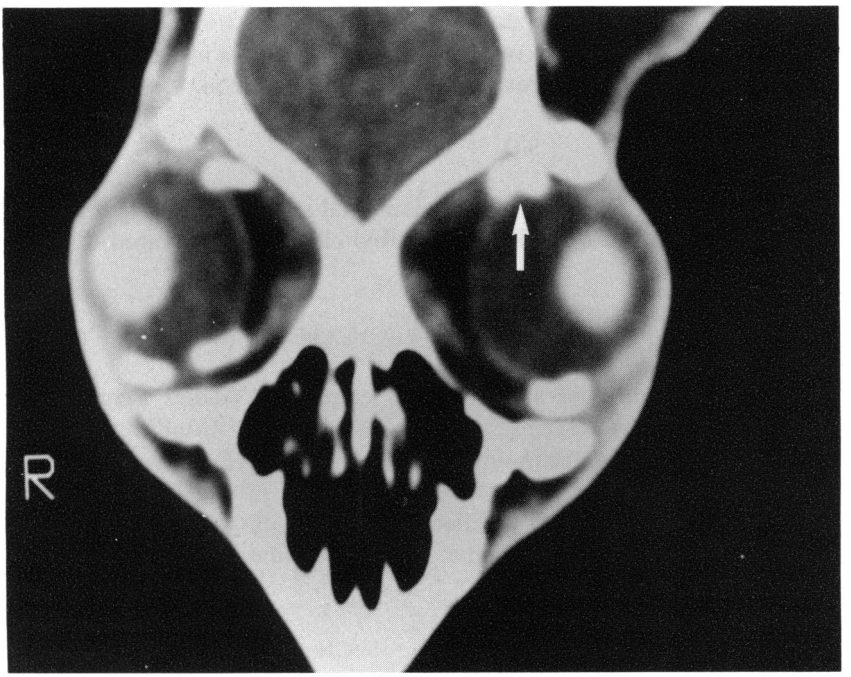
CHEMISTRY OF SILICONES AND THE BIOLOGIC RESPONSE

In reviewing the history of the use of silicones, we see that silicone rubber was rapidly accepted as the material of choice for seton surgery. The polymers of silicone are commonly used in the preparation of prosthetic devices. The use of silicone polymers is based on the following attributes: they are nonallergenic, nontoxic, soft, flexible, durable, nonwettable, and biologically inert. In reviewing the chemistry and biologic reactions of the silicones, one should qualify two of these attributes—nontoxicity and biologic inertness—as being relative phenomena.

FIGURE 2

A: HRP reaction product is seen lining a space between collagen bundles (*black arrows*) of fibrous capsule, and on surface (*open arrow*) of a cross section of collagen bundles (*white arrow*) (× 6000). B: Endothelium (*thin arrow*) is clear visible lining a vessel. HRP reaction product is present within endothelium (*open arrow*), in lumen (*asterisk*), and on surface of a red blood cell (*thick arrow*) (× 10,000).

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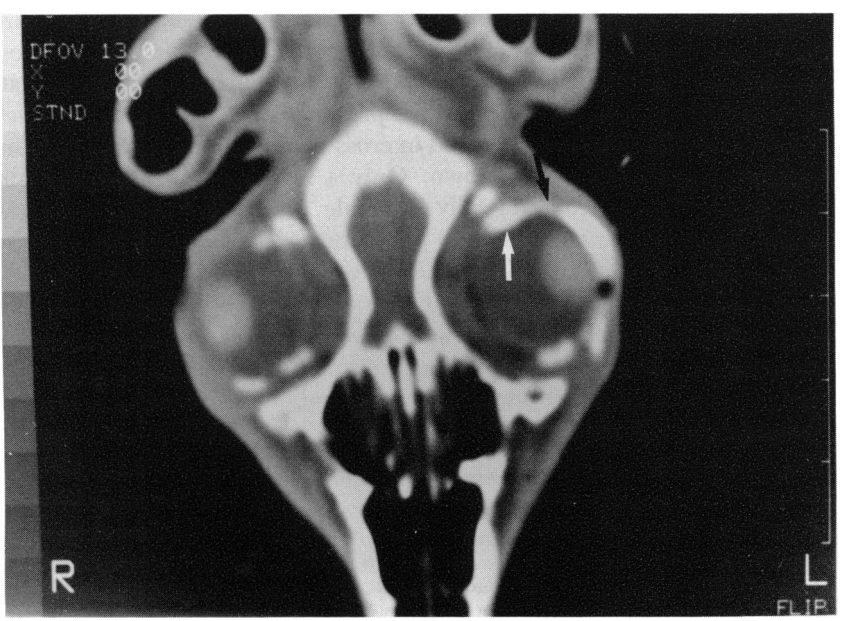
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The synthesis of silicone starts with naturally occurring silicone dioxide (quartz, sand, or quartzite rock).[54] Silicone dioxide is made to react with carbon at high temperatures to yield elemental silicon.

$$SiO_2 + C \rightarrow Si + CO_2$$

The hard, crystalliine, and brittle elemental silicon is subsequently pulverized and reacted directly with methyl chloride at elevated temperatures.

$$6Si + 11CH_3Cl \rightarrow 2SiCl_4 + CH_3SiCl_3 + (CH_3)_2SiCl_2 + (CH_3)_3SiCl + (CH_3)_4Si$$

A mixture of methyl and chloride, containing silanes ranging from tetrachlorosilane to tetramethylsilane, is obtained. Conditions are adjusted to produce a maximum amount of dimethyl dichlorosilane, the monomer for the polydimethylsiloxanes. The resulting liquefied silanes are separated by fractional distillation. Polydimethylsiloxane is prepared by condensation copolymerization of the monomer dimethyldichlorosilane with water.

$$x\,(CH_3)_2SiCl_2 + x\,H_20 \rightarrow -[Si(CH_3)_20-]_x + 2xHCl$$

The primary polymer thus obtained is further processed to yield more complex and specific polymers that can vary in molecular weight, presence or absence of fillers or other additives, type of organic ligans attached to the silicon, and the possible presence of reactive radicals, such as vinyl ligans on silicon to be used in cross linking. About 60,000 silicon-containing compounds are known. Only a few have proved medically useful and become commercially available. Silicones used in artificial organs and implants are primarily polydimethylsiloxanes.

"Medical-grade" silicone elastomers are specifically formulated, manufactured, and qualified for implant uses. Manufacturing and processing are done under carefully controlled, clean conditions to assure a consistent product, free from adulteration and contamination. High-consistency thermosetting medical-grade elastomer compounds are prepared from high molecular-weight polydiorganosiloxanes compounded with high-sur-

FIGURE 3

A: Baseline CT scan showed silicone rubber implants bilaterally. A: Note gutter of 20S band apposed to sclera (*white arrow*). B: Five minutes after injection, dye is seen coursing through Silastic tube (*black arrow*) and beginning to fill space between band and capsule, filling in gutter of band (*white arrow*).

face fumed silica. Silica is the only material known that adequately reinforces the silicone elastomer.

Vulcanization requires the cross-linking of the polymer chains. In one type of cross-linking, silicon-hydrogen ligands, contained as small amounts of methylhydrogensiloxy copolymer in one formulation, react with silicon-vinyl ligands, contained as small amounts of methylvinyl-siloxy copolymer in a second formulation. When the two compounds are blended and heated in the presence of a catalyst, cross-linking occurs. Typical catalysts include trace quantities of rare metals, such as platinum, or organic peroxides. The cross-links are dimethylene bridges covalently bonded between silicon atoms in separate polymer chains. The purpose of cross-linking is to yield a chemically bonded network matrix of primary polymers.

Tests of the biocompatibility of silicones include both short- and long-term tests.[55-57] The short-term tests result in a cumulative toxicity index (CTI). This index is based on testing of the initial material and its extracts by various procedures. In one common procedure, the effect of the silicone material is examined on cells growing in tissue cultures and on the histologic response and degree of hemolysis following implantation of the silicone materials into rabbit muscle. A common test on extracts of silicones includes determination of the zone of lysis in a culture-agar overlay test. This is followed by determining the response on intracutaneous implantation in rabbits, systemic toxicity in mice, and cell-growth inhibition by the aqueous extracts. The CTI is scored between a low of 0 and a high of 1500. As a general rule, material having a CTI of 100 or less is considered to have a low-potential toxic liability. The CTI for silicone rubber was 81, as obtained by Autian.[57]

Although short-term tests for silicone elastomers have shown excellent CTI scores, long-term studies were required to see if the Silastic elastomers would leach toxic materials or if they would degrade and cease to function in the manner desired.

ROLE OF SILICONE IN THE FORMATION OF THE FIBROUS CAPSULE: IN VITRO AND IN VIVO STUDIES

As experience with the ACTSEB procedure developed by Schocket et al[46,47] continued, and several surgical revisions afforded the opportunity to directly observe the fibrous capsule surrounding the No 20S silicone strip, it became clear that the fibrous tissue does not proliferate into or adhere to the groove in the 20S strip, but rather surrounds the entire implant with an oval-shaped capsule nonadherent to the implant. This is fortunate for two reasons: (1) extensive ingrowth would result in consis-

tent ACTSEB failure caused by fibrous blockage of the tip of the Silastic tube that occupies the groove in the 20S strip, and (2) a capsule contiguous with the surrounding tissue but not adherent to the implant itself creates the space that serves as the aqueous-fluid reservoir in the ACTSEB procedure.

It is well established that certain connective tissues, particularly osteocytes, will grow into the pores of an inert porous implant in situ and that the extent and architecture of the ingrowth is dependent upon the pore size.[58] With the potential in mind for disastrous ingrowth of fibrous tissue into the 20S groove, we endeavored to determine the ideal groove width that would allow bridging but not ingrowth. To do so, we decided to avoid the complicating factors found in animal experiments by attempting to grow human scleral fibroblasts in vitro, using plastic vessels modified to include the 20S strip on their floors. However, it soon became clear that fibroblasts neither bridge nor proliferate into the groove in the silicone 20S strip. Indeed, the fibroblasts attached poorly to the silicone material when compared with their attachment to common polystyrene culture vessels.

Qualitative evidence is presented to show that human scleral fibroblasts attach poorly to 20S silicone strips and that attachment is only moderately facilitated by coating the silicone implants with polymerized collagen. This failure of the silicone to become "camouflaged" with an adherent coat of biologically reactive material (fibroblasts) presumably exposes the naked silicone to the surrounding tissue and results in the inflammatory response central to the development of the enveloping fibrous capsule.

Also presented are scanning electron micrographs of the inside surface of a fibrous capsule taken from a rabbit eye with an ACTSEB implant. These micrographs reveal macrophages in addition to collagen fibers and fibroblasts. Macrophages have been implicated as the initiators of the inflammatory response to implanted silicone.[59]

Finally, we present the results of rabbit studies designed to elucidate the formation of the fibrous capsule and the role of the silicone implant itself in the capsule architecture.

Materials and Methods

Initiation of Human Scleral Fibroblast Cell Line.—Human scleral-episcleral tissue was obtained from an adult eye within 6 hours postmortem and suspended in chilled, balanced salt solution (BSS) for transport. Using sterile technique, 1 × 1-mm pieces of sclera were placed in 35-mm diameter culture dishes (Falcon) containing 2 ml of fresh cell medium (minimum essental medium with Hanks' salt solution base) supplemented

with 10% (v/v) fetal bovine serum, 1% (v/v) penicillin-streptomycin, and 0.25% (v/v) fungizone. The tissue pieces were mechanically disaggregated, using a surgical blade and fine forceps, and placed in a humidified atmosphere at 37.5°C and 5% CO_2 tension.

The medium was changed every 2 to 3 days until fibroblasts migrating out of the scleral-episcleral explant had become fully confluent (about 2 weeks), at which time the cells were subcultured into 75-ml tissue-culture flasks (Falcon). Cells were then passaged every 10 to 14 days and medium was changed every 4 to 5 days. With each passage an aliquot of the fibroblast suspension was placed in a standard dimethyl sulfoxide (DMSO) freezing solution for storage at −135°C.

Modification of Culture Dishes with Silicone and Collagen.—Lengths of No 20S silicone-strip implant, identical to those used in the ACTSEB procedure (Medical Instruments Research Associates), were rinsed with sterile distilled water, autoclaved, and fastened to the polystyrene floor of 35-mm diameter culture dishes using silicone cement (Dow Corning) under sterile conditions.

For preparation of silicone implants covered with a thin adherent film of collagen, commercially available bovine dermal collagen (Vitrogen 100^R, Polysciences) was prepared as an isotonic, pH 7.4 solution with phosphate-buffered saline. This collagen solution was used to cover some of the silicone-modified dishes described above. The dishes were incubated for 10 to 20 minutes at 37°C to promote gelatin and were then transferred to a laminar flow hood for drying overnight. Finally, the collagen film was rinsed with sterile water to remove salts and rehydrate the film.

Growth of Fibroblasts in Modified Culture Dishes.—Cells of passage No 14 were added to experimental dishes (modified to include 20S implants, some collagen-coated) and control dishes (plain polystyrene) using an inoculum of 10^5 cells per dish. Medium was changed every 4 to 5 days.

Microphotography was performed with a Zeiss inverted microscope equipped for 35-mm photography. All photographs were made with normal brightfield optics, using a green contrast filter.

When the attachment of the fibroblasts to the silicone strips had qualitatively reached a plateau (approximately 10 days after inoculation), the silicone strips were gently peeled away from the polystyrene dishes, placed in a solution of 4% formaldehyde and 1% glutaraldehyde, and were submitted for scanning electron microscope preparation. All microscopy was performed with an AM Ray 1000 model scanning electron microscope.

Scanning Electron Microscopy of Fibrous Capsule.—An albino rabbit on which the ACTSEB procedure had been performed 5 weeks previously was killed with a pentobarbital (Nembutal) overdose and the ACTSEB eye carefully enucleated. Following dissection of the conjunctiva and extraocular muscles, a sample of the fibrous capsule enveloping the 20S encircling strip was placed in a solution of 4% formaldehyde and 1% glutaraldehyde and submitted for scanning electron microscopy, as described previously.

Fibrous Capsule Studies.—Rabbits were randomly assigned to undergo the ACTSEB procedure with one of several configurations of the implant:

1. No 20S silicone band (Medical Instruments Research Associates [MIRA]).
2. Heparinized No 20S silicone band (MIRA).
3. Tolentino-style hydrogel implant (Miragel).
4. Flat (No 240) silicone band (MIRA).
5. A No 20S silicone band, with the orbital end of the Silastic tube left excessively long.
6. A No 20S silicone band (MIRA) with a 5-mm hole cut in the gutter.
7. Multiple holes of diameters ranging from 50 μm to 100 μm were made in the wall of a 2-mm Silastic tube using an argon laser (Coherent) at a setting of 3 W for 3 to 8 seconds. The penetration of the wall was facilitated by marking the tube with black ink prior to laser use. A 0.6-mm Silastic tube (Storz) was then cemented into the lumen of the larger tube with silicone cement (Dow).

The ACTSEB procedures were otherwise performed by the methodology described previously. After 5 months, the animals were sacrificed by Nembutal overdose, and the eyes were enucleated for immediate dissection under the operating microscope and subsequent histopathologic study, using hematoxylin and eosin staining.

Results

Cell Culture Studies.—For a culture of cells to reach 100% confluency on a given substrate, two obstacles must be overcome: (1) the cells must attach to the substrate, and (2) the cells must divide through mitosis until the upper limits of cell-cell contact inhibition are reached. In general, cell attachment is complete within 6 to 48 hours, and complete confluency is reached within 10 to 14 days.

Human scleral-episcleral fibroblasts passaged into common polystyrene culture vessels attach and divided exuberantly (Figs 4 and 5). Silicone, however, does not permit fibroblast attachment at 48 hours (Fig 6) and, even after 2 weeks, few fibroblasts have attached to the implant (Fig 7). In

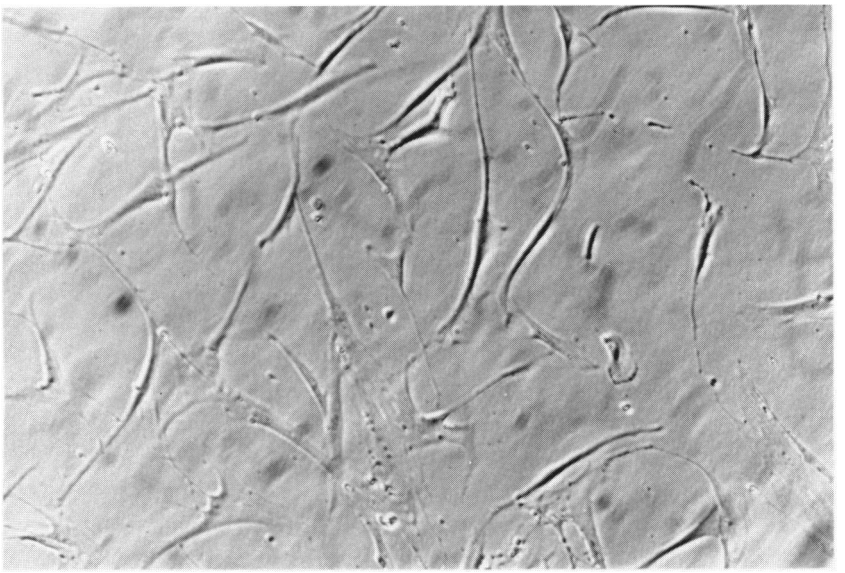


FIGURE 4
Human scleral fibroblasts attaching to floor of polystyrene culture dish 48 hours after subculture (× 200).

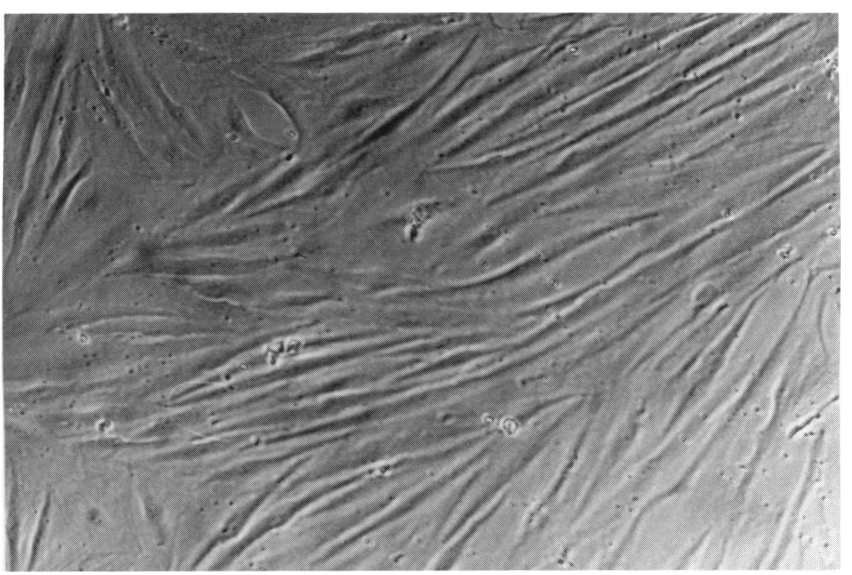


FIGURE 5
Human scleral fibroblasts attaching to polystyrene culture dish floor 14 days after subculture (× 200).

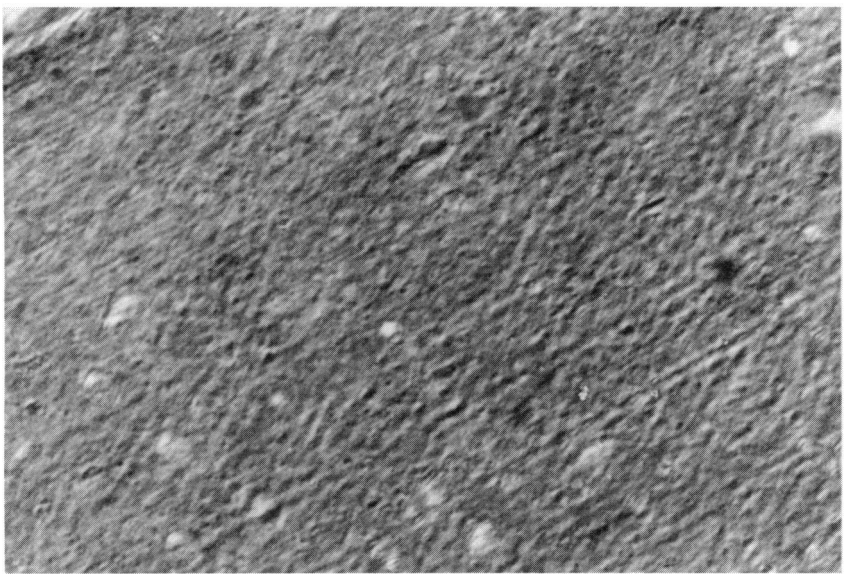


FIGURE 6
Human scleral fibroblasts have not attached to groove of a plain 20S silicone strip 48 hours after subculture (× 200).

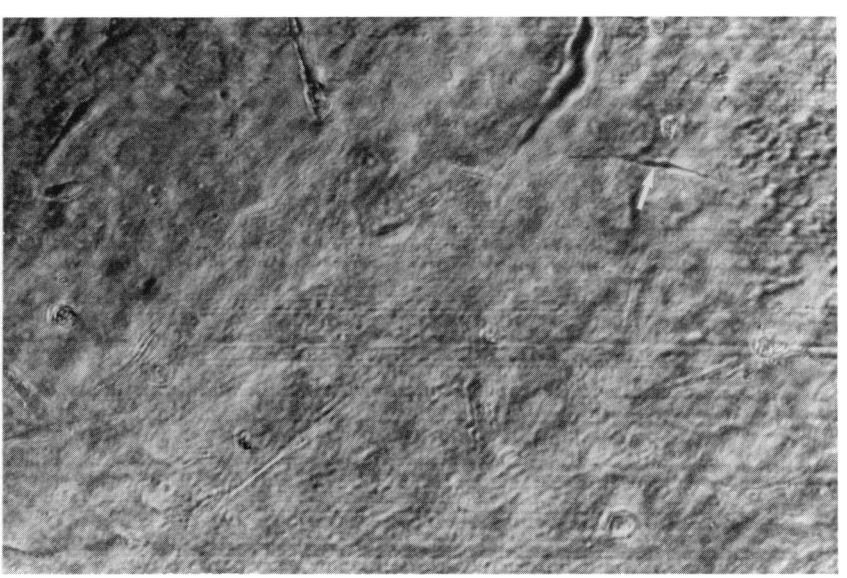


FIGURE 7
Few human scleral fibroblasts (an individual cell is indicated by *arrow*) have attached to groove of a plain 20S silicone strip 14 days after subculture (× 200).

fact, the number of attached fibroblasts remained low for up to 2 months, when the culture was finally discarded. It is as if the few cells that had succeeded in adhering to the silicone were somehow rendered unable to enter the mitotic phase of the cell cycle.

When the silicone is covered with a thin layer of bovine dermal collagen, fibroblasts are able to attach; the number of cells attached to substrate at 48 hours (Fig 8) does not differ significantly from the number attached to polystyrene at 14 days (Fig 9). As was the case for plain silicone, the attached fibroblasts seem to be locked in the G1 phase, unable to enter into mitosis.

Scanning electron micrographs of the fibroblasts attaching to the surface of the silicone 20S strip provide more evidence that the cells adhere poorly to the silicone substrate. Figs 10 and 11 show a complete fibroblast and a fragment of one, respectively. In both micrographs, it is clear that the fibroblast has little chance of gaining anything more than a tenuous grip on the strikingly irregular surface of the medical-grade silicone. Fig 12 shows another fibroblast that was apparently unable to attach firmly to the silicone substrate.

Fibrous Capsule Studies.—Fig 13 shows a scanning electron micrograph of the inner surface of a rabbit fibrous capsule formed around an ACTSEB implant. At the center is seen what is morphologically most consistent with an aggregation of macrophages, presumably embedded in the capsule and reacting against the silicone implant. This is similar to a scanning electron micrograph shown in Kossovsky's[59] study of recovered silicone mammary prostheses and identified as showing macrophage aggregates. Figs 14 and 15 are also scanning electron micrographs of the capsule and demonstrate the presence of fibroblasts and collagen.

Figs 16 to 18 demonstrate the different fibrous-capsule densities that result from various implants used in performing the ACTSEB procedure on rabbits. It should be noted that the fibrous tissue induced by the heparin-coated silicone band is the least dense (Fig 17).

One of the rabbit's eyes with a functioning ACTSEB revealed minimally vascularized connective-tissue ingrowth toward the outer portion of the Silastic band (Fig 19A, arrows). The silicone-rubber columns of the gutter sharply delimited the mound of vascularized connective tissue. No vascularization could be seen where the silicone-rubber columns abutted the sclera (asterisk).

Histologic section (Fig 19B) revealed a plate of connective-tissue ingrowth (arrow). The encapsulated Silastic-tube cavity (asterisk) is visible beneath the band, indicating that the Silastic tube is close to connecting with the cavity beneath the band.

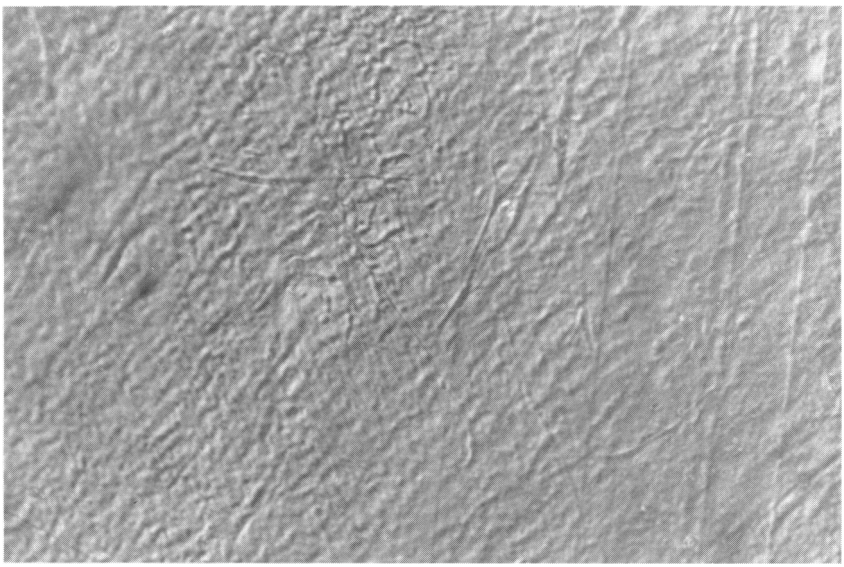


FIGURE 8
Human scleral fibroblasts attaching to collagen-coated groove of 20S silicone strip 48 hours after subculture (× 200).

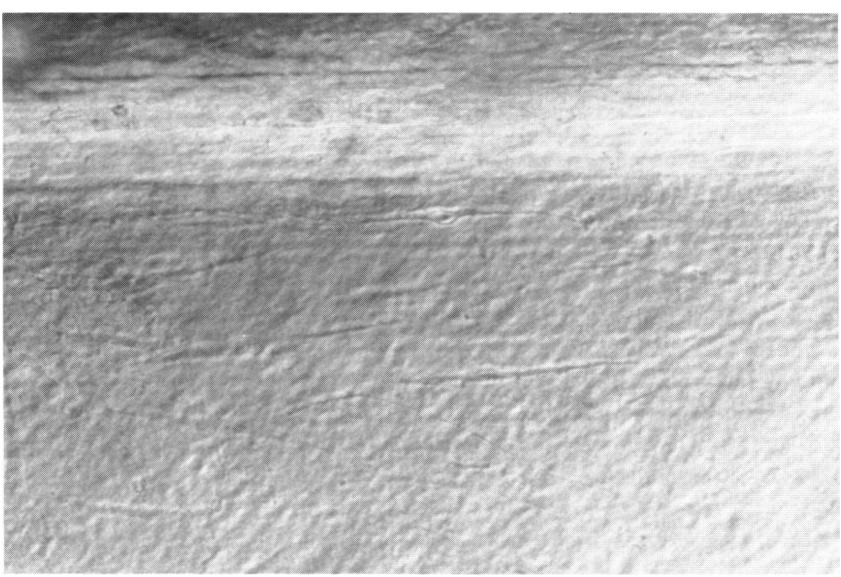


FIGURE 9
Human scleral fibroblasts attaching to collagen-coated groove of 20S silicone strip 14 days after subculture (× 200).

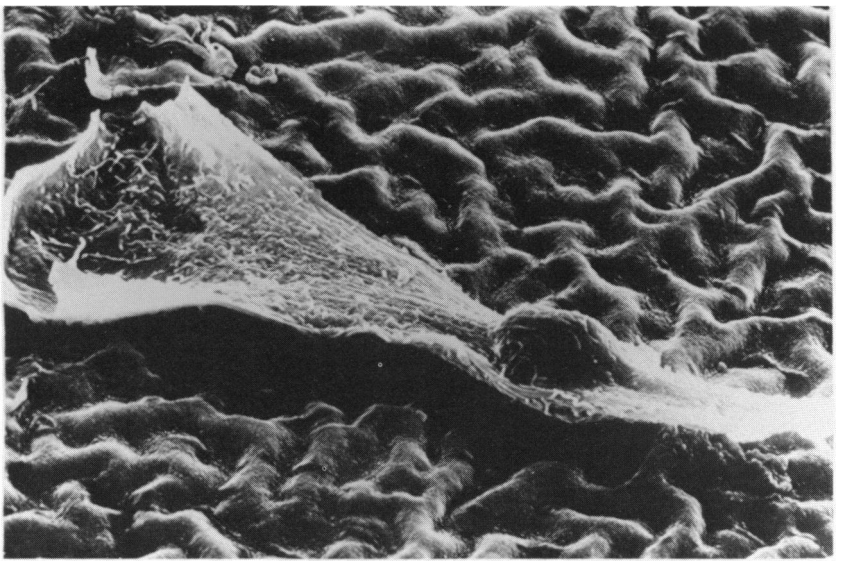


FIGURE 10
Scanning electron micrograph of a human scleral fibroblast tenuously attached to irregular surface of a 20S silicone strip (× 2000).

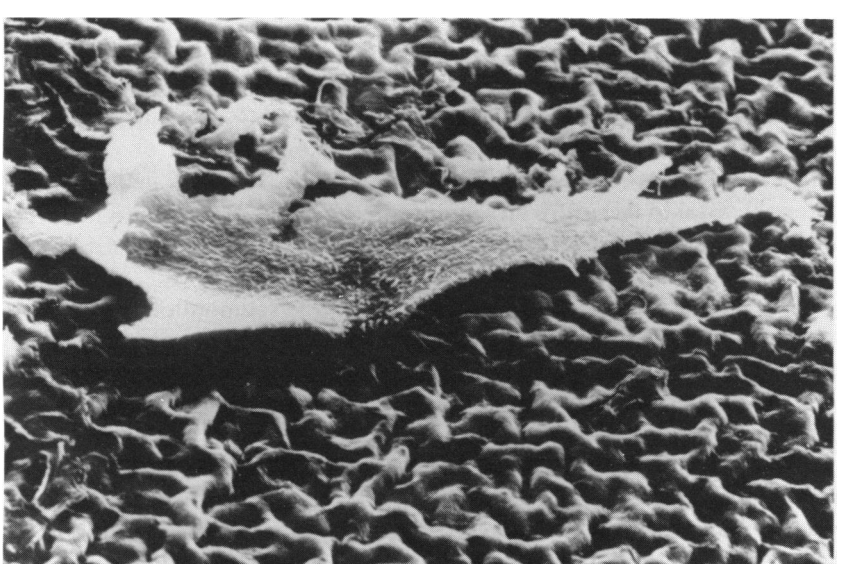


FIGURE 11
Scanning electron micrograph of a cellular fragment clinging to a 20S silicone strip (× 2000).

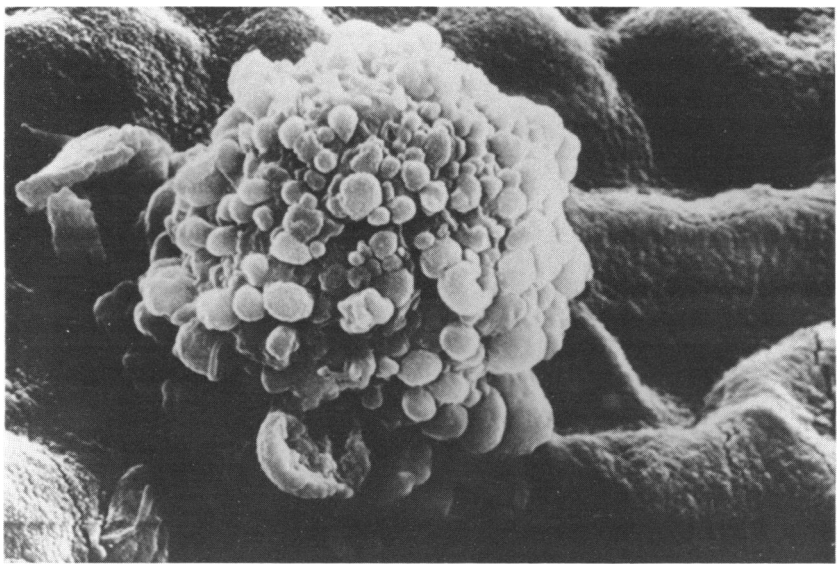


FIGURE 12
Scanning electron micrograph of a dead fibroblast that has become rounded after failing to attach to irregular surface of a 20S silicone strip (× 5000).

The rabbit eyes revealed encapsulation of the Silastic tube except where the sutures held the tube to the band (Fig 19C). A probe defines the unencapsulated tube. The Silastic tube can be seen buried under connective tissue on both sides of the sutures (arrows).

In the rabbit eye shown in Fig 19D, the tube becomes encapsulated (asterisk) distal to its suture attachment to the 20S gutter, where it is free to come into contact with the episclera but remains unencapsulated (arrow) where the tube was sutured to the 20S band.

In the gutter area of a 20S band, where a large segment of silicone was removed, one can see a heavy ingrowth (asterisk) of fibrous connective tissue (Fig 19E). The corresponding histologic section (Fig 19F) reveals the hole to be completely filled with vascularized connective tissue and inflammatory cells (arrows).

Fig 20A shows a 2-mm Silastic tube with holes of diameters ranging from 50 to 500 μm, fashioned by laser. When the encircling element was exposed 3 months postoperatively (Fig 20B), a purulent-appearing fluid was seen filling the lumen. Careful dissection revealed no ingrowth into the 50-μm holes but extensive ingrowth into holes of 100 μm or larger (arrow).

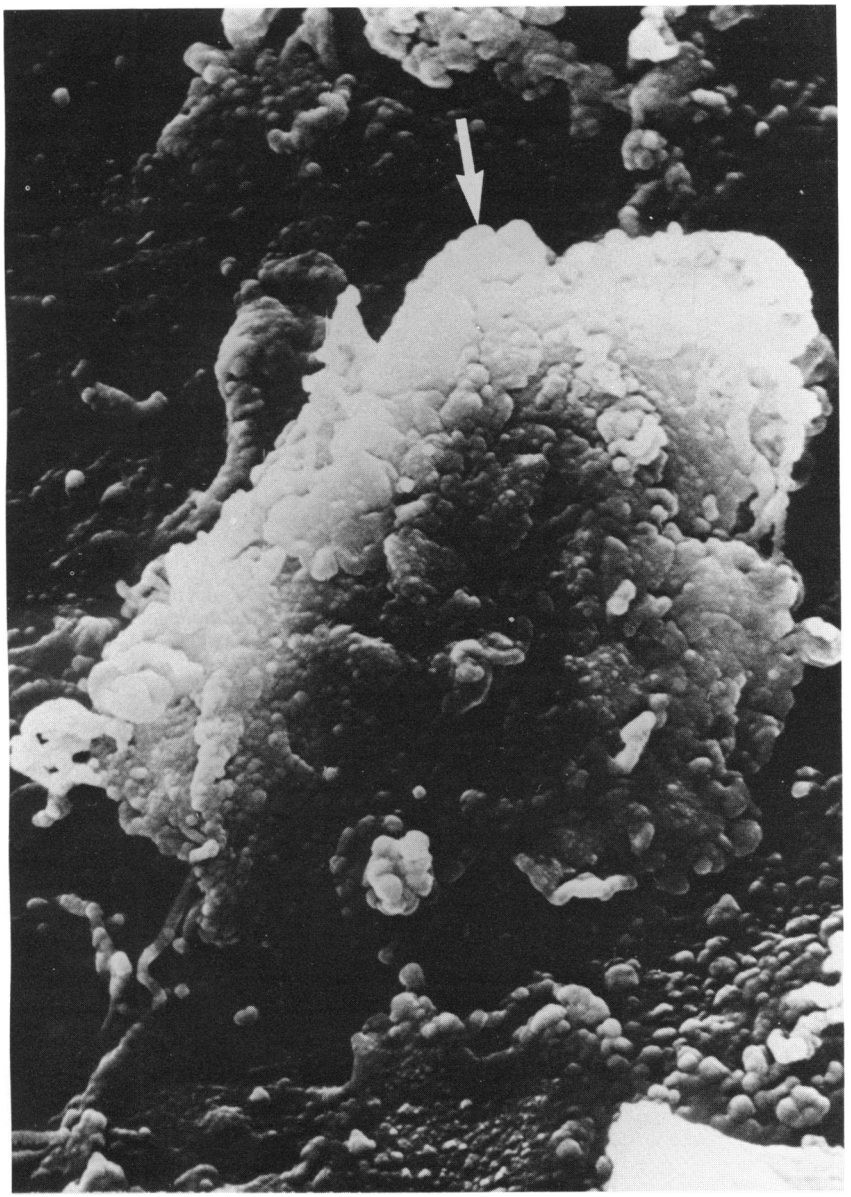


FIGURE 13
Scanning electron micrograph of inner surface of fibrous capsule taken from a rabbit ACTSEB. Cellular aggregates morphologically consistent with macrophages (*arrow*) are embedded within capsule surface (× 5000).

FIGURE 14
Scanning electron micrograph of inner surface of fibrous capsule taken from a rabbit ACTSEB. Note presence of two fibroblasts (*thick arrows*) with abundant collagen fibers (*thin arrows*) interwoven throughout (× 1000).

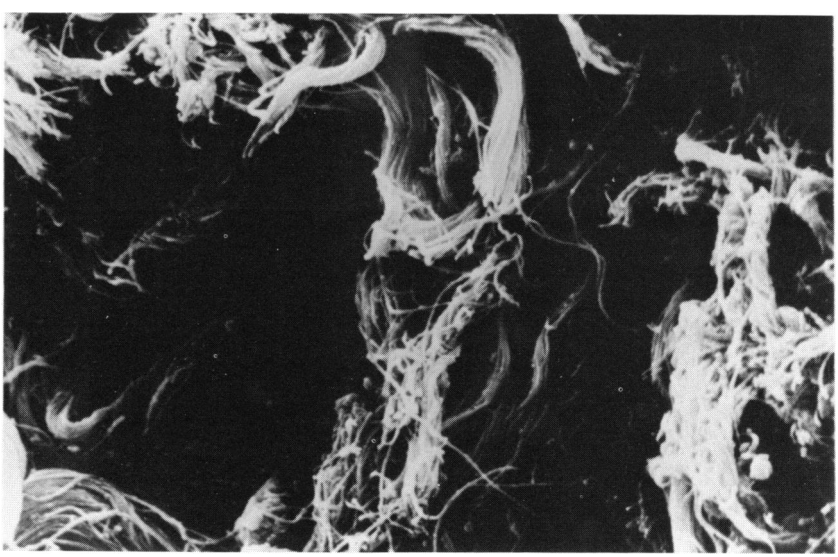


FIGURE 15
Scanning electron micrograph of inner surface of fibrous capsule taken from a rabbit ACTSEB. Collagen fibers, many arranged in bundles, snake through fibrous tissue (× 5000).

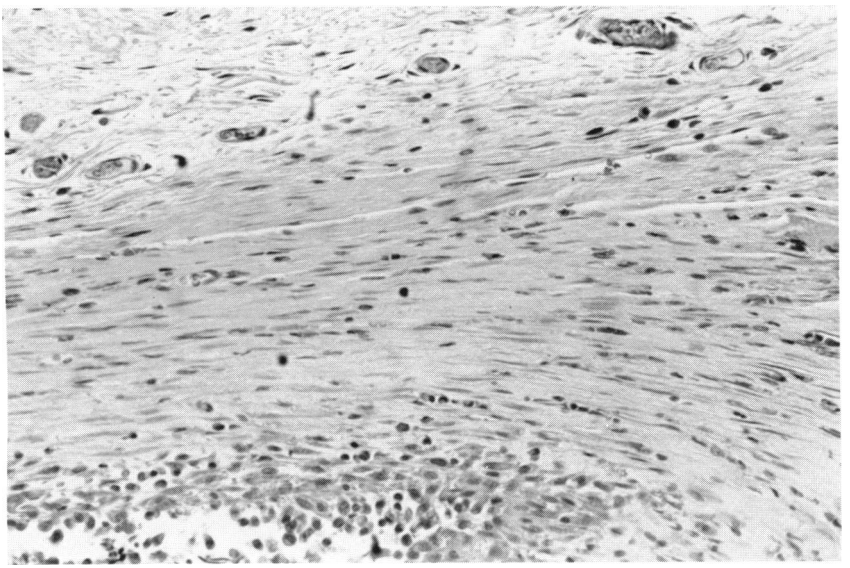


FIGURE 16
Light micrograph showing density of fibrous capsule formed around a plain 20S silicone strip in a rabbit ACTSEB (× 200).

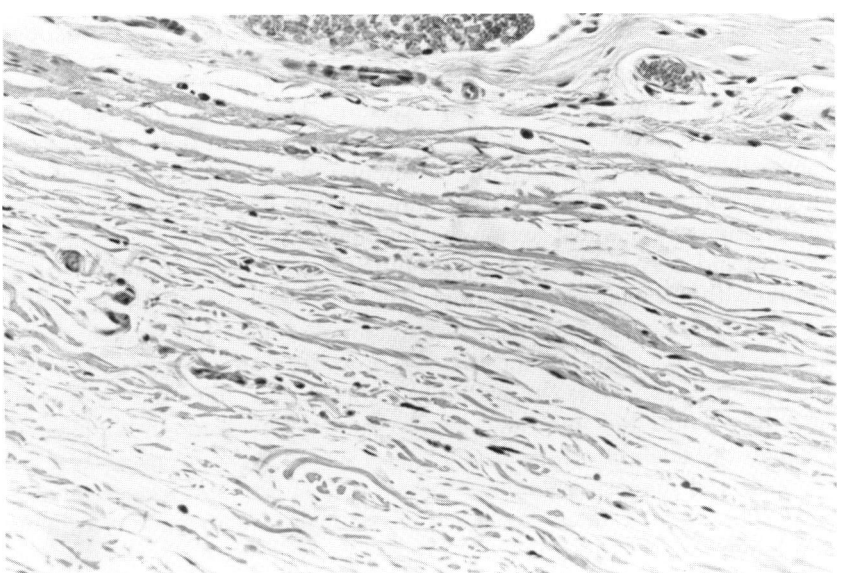


FIGURE 17
Light micrograph showing density of fibrous capsule formed around a heparinized 20S silicone strip in a rabbit ACTSEB (× 200).

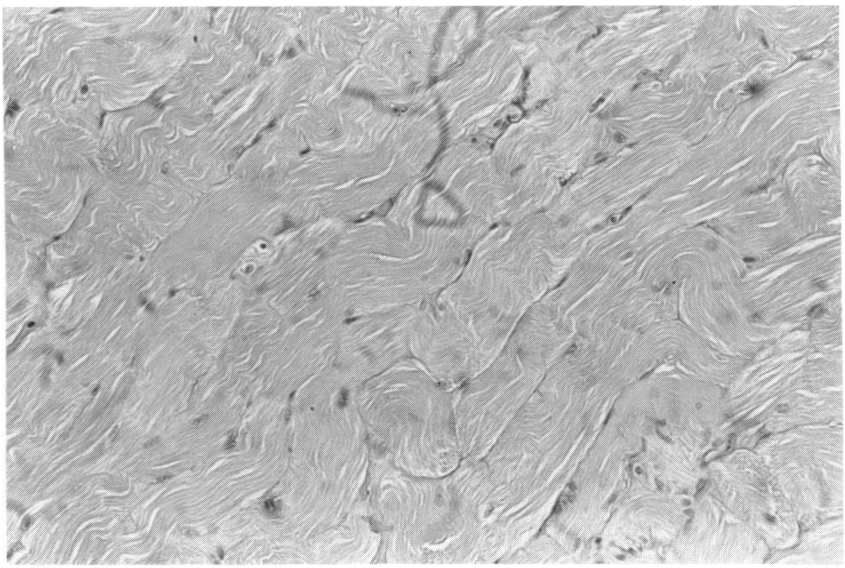


FIGURE 18
Light micrograph showing density of fibrous capsule formed around a plain Tolentino hydrogel implant in a rabbit ACTSEB (× 200).

TECHNIQUES TO AVOID COMPLICATIONS AND FAILURE IN THE ACTSEB PROCEDURE

IOP has been successfully controlled in severe neovascular glaucoma patients by using the ACTSEB procedure. Despite its high degree of success, there are several technical problems inherent in the procedure, especially in those patients with neovascular glaucoma, and there are also surgical failures for which no explanation can be provided. Of the technical problems, the most serious is hyphema, which can lead to blood clotting and may result in blockage of the lumen of the seton or organization within the anterior chamber. The organized blood induces further vascularization of the anterior segment and eliminates any hope of restoring the patient's sight. Performing the procedure on patients with severe rubeosis iridis presents the potential for hyphema, since the instrument introduced into the anterior chamber must pass through the heavily vascularized chamber angle. Even after a successful shunt procedure and regression of rubeosis secondary to lowering of IOP and panretinal ablation, subsequent cataract surgery can result in a recurrence of rubeosis and hyphema.

A major problem of seton-drainage procedures is hypotony developing during the first 2 weeks following surgery. When hypotony occurs in an eye that has had prior surgery, hemorrhagic choroidal detachments may

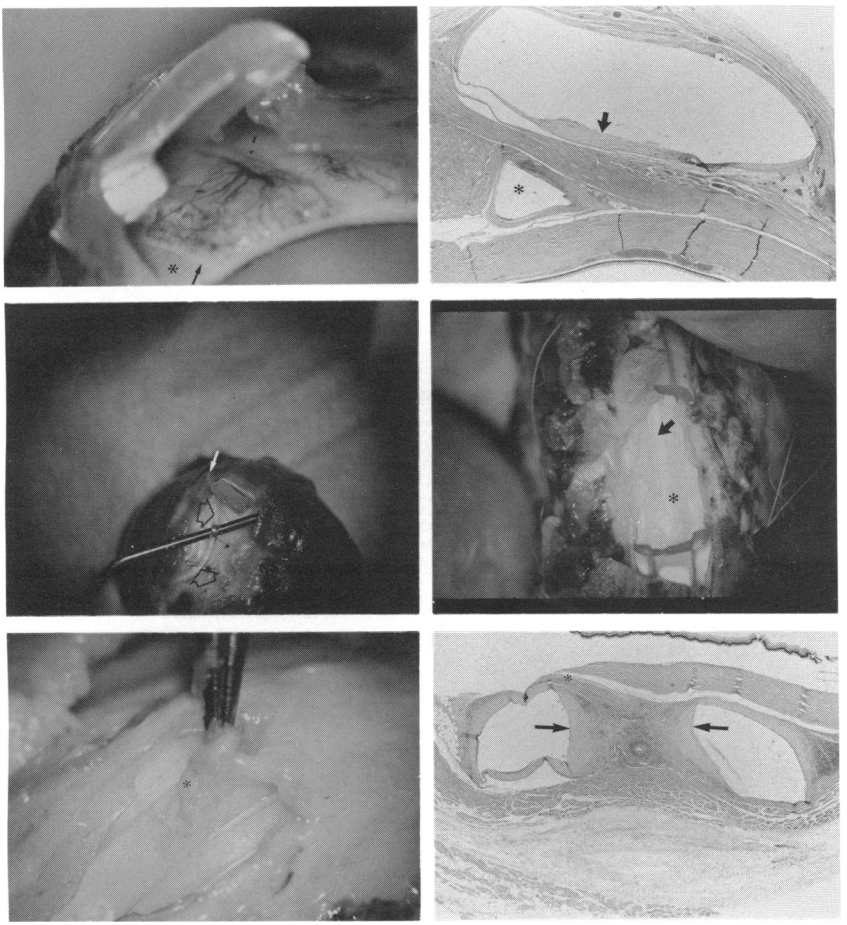


FIGURE 19

A: A plate of vascularized ingrowth (*arrows*) is seen to be sharply delimited by columns of 20S band. Note relative avascularity of sclera abutting on silicone rubber columns (*asterisks*). B: Histologic section showing connective tissue ingrowth partially filling gutter of 20S band (*arrow*). Note encapsulated Silastic tube cavity (*asterisk*) below band (× 20). C: Silastic tube is encapsulated (*open arrow*) on both sides of sutures. Probe defines nonencapsulated segment that was apposed to band. *White arrow* defines connective tissue cap overgrowing orbital end of Silastic tube. D: Tube is unencapsulated (*arrow*) where it was apposed to 20S band by a suture, but becomes encapsulated (*asterisk*) where tube end was unsupported by a suture, allowing contact with episclera. E: A connective tissue ingrowth (*asterisk*) from episclera is seen penetrating a hole in gutter of 20S band. F: A vascularized connective tissue stalk is seen emanating from episclera (*asterisk*) with inflammatory cells completely filling hole in silicone (*arrows*) (× 20).

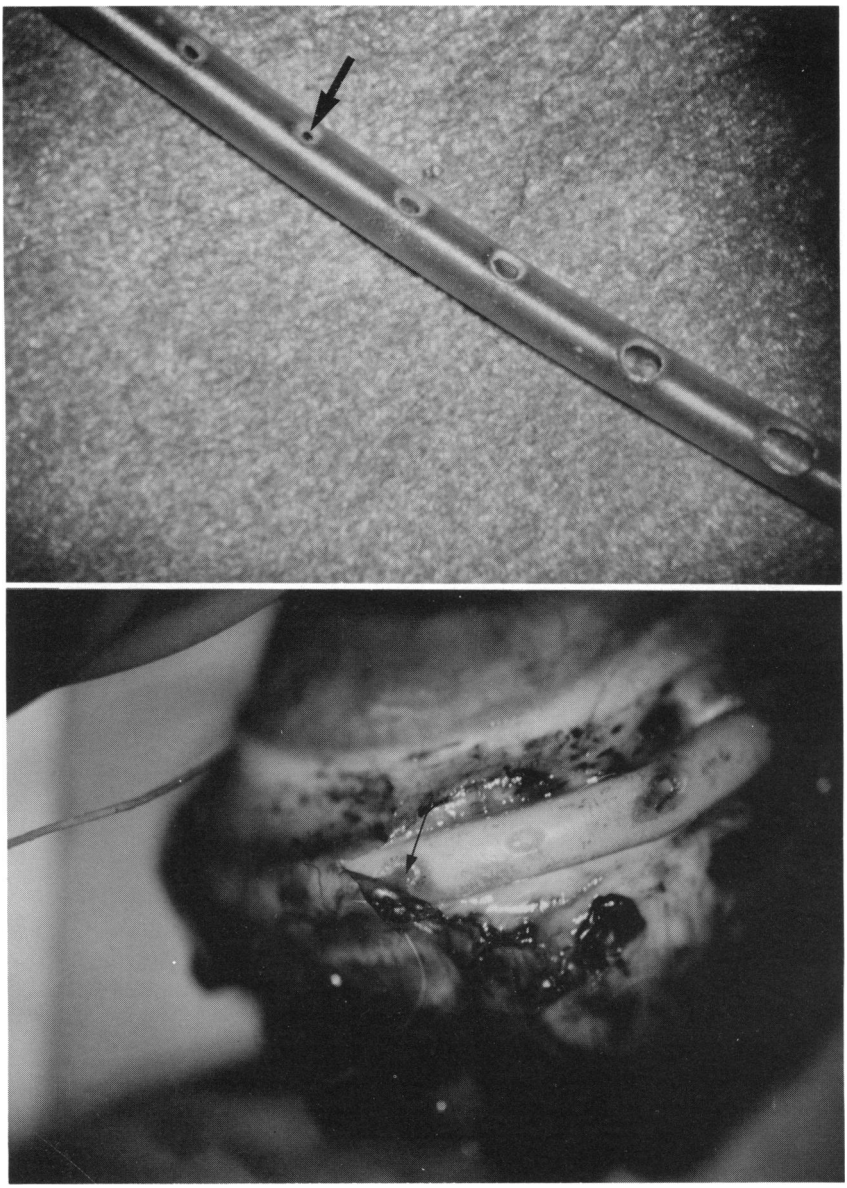


FIGURE 20

A: Silastic tube in which holes ranging in size from 50 μm (*arrow*) to 500 μm were fashioned with argon laser. B: Encircling element, 3 months postoperatively, shows a purulent appearing fluid in lumen. Careful dissection revealed ingrowth into holes of 100 μm or larger (*arrow*).

occur with resultant loss of vision. We have seen this unfortunate complication in 4 of 75 neovascular glaucoma patients upon whom shunt procedures were performed. Unidirectional valves have been used, but the disadvantages of high monetary cost and potential for obstruction using these valves have prompted a quest for a better solution to the hypotony problem.

Another potential cause of ACTSEB failure is occlusion of the terminal tip or fibrous blockage of the orbital end of the Silastic tube by connective tissue.

In this section of the study, both clinical and histopathologic evidence is presented to show that these complications can be largely avoided by applying several simple modifications to the ACTSEB procedure.

HYPHEMA AND BLOOD CLOTS OBSTRUCTING THE TUBE LUMEN

Anterior Chamber Entry Using a Needle Cautery

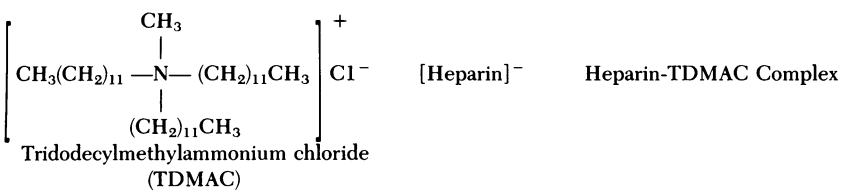
Materials and Methods. A 25-gauge needle is introduced into the anterior chamber through the limbal area under a scleral flap, at an angle parallel to the iris. To prevent hyphema caused by entry into a highly neovascularized angle, the needle is touched with a wet-field cautery (Mentor) at a setting of 30, which results in coagulation of the bleeding angle vessels. The 25-gauge needle is then withdrawn, the anterior chamber is restored with hyaluronic acid (Healon), and the procedure is repeated with a 23-gauge needle. Anterior dissection of the scleral flap into 1 mm of clear cornea allows excellent visualization of the needle tract through the sclera. The Silastic tube can be pinched closed with Shepard microforceps and introduced through the opening into the anterior chamber. The tube then expands in the needle tract, making a snug fit and minimizing aqueous loss.

Results. In the last 20 neovascular glaucoma patients for which this procedure was used, none have bled during tube insertion after coagulation of the entry tract from the adjacent vascularized angle. Small areas of peripheral iris blood staining have resulted from the sudden decompression of the glaucomatous eyes or from the manipulation of the eye during surgery. These hemorrhages have not resulted in a hyphema and were completely cleared on the first postoperative examination.

Permanent Heparinization of Silastic Tubes in an Attempt to Reduce Thrombogenicity in the ACTSEB Procedure

The permanent fixation of a heparin complex to a variety of plastics and rubbers has proved to be an effective means of creating nonthrombogenic surfaces.[60] The process consists of immersion of the device in a solution of

heparin-quaternary ammonium compound-complex in an organic solvent, removal of the organic solvent, and sterilization by gas or heat. The amount of complex fixed to the surface is reported to be about 40 $\mu g/cm^2$; this surface concentration is controlled by the concentration of the complex and the duration of the immersion. The complex between heparin and tridodecylmethylammonium chloride (TDMAC) is formed when heparin, an acid mucopolysaccharide with an overall negative charge, is exposed to the TDMAC ammonium ion, which is positively charged.



Tridodecylmethylammonium chloride (TDMAC)

During the immersion process, the surface of the silicone polymer is swollen by the organic solvent, allowing penetration of the polymer surface by the hydrophobic hydrocarbon chains of the TDMAC portion of the complex. Removal of the organic solvent by evaporation results in firm fixation of the complex to the polymer surface as the polymer shrinks back to normal size. The surface-bound complex on polymers such as silicones, vinyls, and methacrylates is resistant to elution by saline or blood. Surface-bound heparin apparently causes thromboresistance in the same way as does heparin in solution. This conservation of function has been likened to preservation of activity in a surface-bound enzyme. The presence of heparin on the surface of the silicone polymer probably simulates the naturally occurring heparin coat of the endothelium. The presence of the heparin decreases protein, leukocytes, and platelet adherence, resulting in prolonged coagulation time.[61]

Cannulas treated with the heparin-TDMAC complex are routinely used as aortic and carotid shunts in vascular surgery, as drainage tubes in the management of chronic ascites, and as long-term implants in applications such as hyperalimentation lines and Hickman catheters.[62,63] This report documents the application of the heparin-TDMAC complex-fixation process to the Silastic tubing using in the ACTSEB procedure and demonstrates its effectiveness in creating a stable, nonthrombogenic surface environment. Preliminary results of in vitro cytotoxicity testing of heparinized silicone are also presented.

Materials and Methods

Heparinization of Tubes. Sections (5 cm) of Silastic tubing 0.30-mm inner

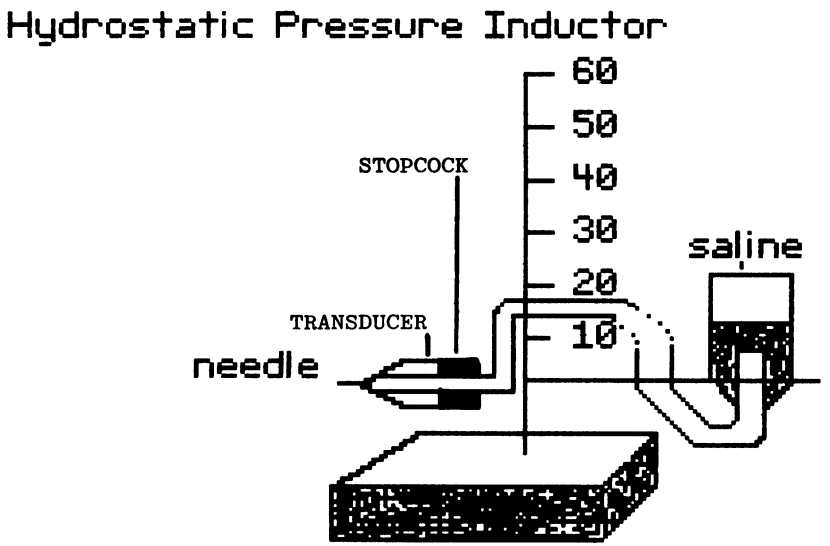


FIGURE 21
Hydrostatic pressure apparatus that induces a variable pressure from 10 to 60 mm Hg in the lumen of a 25-gauge needle by elevating saline container.

and 0.64-mm outer diameter (Storz) were treated on all surfaces with a 1% solution of the heparin-TDMAC complex (Polysciences) in 1:1 toluene/petroleum ether at room temperature for 30 to 60 seconds. The tubes were then flushed with compressed air and dried overnight in a vacuum oven to remove traces of the volatile organic solvent.

An apparatus was constructed, consisting of a bottle of normal saline secured to a column by an adjustable clamp (Fig 21). Tubing connected the saline bottle through a pressure transducer and adjustable stopcock to a 25-gauge needle. It was possible to calibrate the column so that a given height of the saline bottle above the level of the 25-gauge needle gave a known pressure of saline flowing from the needle. The height of the column translated into an available pressure range of 10 to 60 mm Hg in the 25-gauge needle.

Whole blood was obtained from a healthy subject and immediately used to fill equal lengths of heparinized and untreated (control) Silastic tubing. At various times after filling, the tubes were placed on the 25-gauge needle and, beginning with a bottle height calibrated to give 10 mm Hg pressure in the needle, the stopcock was opened and the time required for the entire length of the tube to be emptied of blood was recorded. If no movement of blood from the tube was observed after 1

minute, the stopcock was closed while the bottle height was increased in 10-mm Hg increments; emptying was then attempted at the higher pressure. This was continued until the blood was evacuated from the tube or the maximum pressure of 60 mm Hg was reached.

The heparinized and control Silastic tubes used in the experiment were flushed repeatedly with normal saline and distilled water and dried in a stream of compressed air. The experiment was then repeated using these same tubes.

Results

Thrombus-Inhibition Testing of Heparinized Tubes. The results of the initial test and repeat test are summarized in Tables I and II, respectively. It should be noted that in every instance the heparinized tubes required only the minimum pressure of 10 mm Hg for evacuation of blood, whereas the control tubes always required higher pressure or more time for evacuation (or both) and, in fact, would not empty even at the maximum pressure of 60 mm Hg for most of the time points.

Clinical Trial with the Heparinized Silastic Tube

After preliminary in vitro (fibroblast cultures) and in vivo (rabbit) studies had excluded any detectable degree of toxicity associated with Silastic

TABLE I: INITIAL TEST: CONDITIONS REQUIRED TO EMPTY BLOOD-FILLED HEPARINIZED AND NONHEPARINIZED SILASTIC TUBES

TIME AFTER FILLING (min)	HEPARINIZED		NONHEPARINIZED	
	mm Hg	TIME (sec)	mm Hg	TIME (sec)
15	10	1	10	3
20	10	1	10	3
30	10	2	*	
40	10	2	*	

*Tube could not be evacuated at maximum pressure of 60 mm Hg for 10 minutes.

TABLE II: REPEAT TEST: CONDITIONS REQUIRED TO EMPTY BLOOD-FILLED HEPARINIZED AND NONHEPARINIZED SILASTIC TUBES FOLLOWING USE IN THE INITIAL TEST (TABLE I) AND AFTER VIG OROUS WASHING

TIME AFTER FILLING (min)	HEPARINIZED		NONHEPARINIZED	
	mm Hg	TIME (sec)	mm Hg	TIME (sec)
15	10	4	60	5
20	10	3	*	
30	10	3	*	
40	10	3	*	

*Tube could not be evacuated at maximum pressure of 60 mm Hg for 10 minutes.

tubes heparinized by the heparin-TDMAC complex method described above, it was decided to use the tubes in ACTSEB procedures performed on patients with severe refractory glaucoma.

Materials and Methods

Twenty patients with severe, medically uncontrolled neovascular glaucoma and rubeosis iridis underwent, after informed consent, the ACTSEB procedure performed by the author. Randomly assigned permanent intraluminally heparinized Silastic tubes were used. The surgeon had no knowledge of which tubes were heparinized and which were not. Postoperatively, patients were evaluated daily for 4 days, weekly for the next 4 weeks, and then monthly for the next 4 months. Evaluation included slit-lamp grading on a 1+ to 4+ scale of conjunctival hyperemia, aqueous cells and flare, and fibrous deposition around the anterior chamber portion of the Silastic tube.

Results

Levels 1+ to 3+ of cells and flare and hyperemia were noted postoperatively in both groups, without any significant difference in slit-lamp grading between the two. No hyphema or fibrin deposition around the tube occurred. After a 5-month follow-up, all of the patients are well controlled (IOP $\leq$ 20 mm Hg) without the need for further medical treatment.

HYPOTONY

Hypotony has occurred following the ACTSEB procedure during the postoperative period in which the capsule forms around the encircling band (1 to 2 weeks).[46] After the capsule forms, IOP remains in a remarkably narrow range (14 to 20 mm Hg). Therefore, excessive aqueous drainage through the seton should be limited only for the first 2 weeks postoperatively. This was accomplished in four patients by the following method: After the ACTSEB placement had been completed, but before Tenon's and conjunctival closure, a 4-0 catgut double-arm suture was passed beneath the Silastic tube just posterior to the scleral flap. The sutures were then brought through the overlying Tenon's and conjunctiva and tied, obliterating the tube lumen. A separate Tenon's and conjunctival closure was then carried out as previously described.

The anterior chamber of all four eyes remained fully formed after surgery, and IOP on the first day was between 15 and 20 mm Hg. The IOP gradually increased 5 to 10 mm Hg during the second week. At this time, the suture was easily excised. The IOP immediately dopped 4 to 5 mm Hg and, over the next few days, returned to between 14 and 18 mm Hg.

FIBROUS ENCAPSULATION OF THE ORBITAL END OF THE SILASTIC TUBE

I have revised ten eyes that have had a functional ACTSEB several months postoperatively, at which time the IOP has risen to unacceptable levels between 30 and 50 mm Hg. Clinical evaluation has shown a quiet eye with a well-placed, patent anterior chamber Silastic tube. On revision, the distal Silastic tube opening has been found to be encapsulated by fibrous tissue only where the tube is not in juxtaposition with the encircling band. In a recently revised ACTSEB 1 year after surgery, the Silastic tube was traced from the exit beneath the scleral flap to the distal opening. The Silastic tube was found to be totally encapsulated from the scleral flap to the point beneath the gutter of the encircling band. At this point, the Silastic tube ascended to its point of fixation to the Silastic band with 8-0 nylon. Encapsulation of the tube stopped completely 1 mm from the dome of the gutter on the approach to suture fixation to the 20S band. Approximately 10 mm distal to the first suture, the nylon suture was degraded and fragmented, allowing the Silastic tube to touch the episclera beneath the gutter of the encircling band. The Silastic tube beneath the 20S band (Fig 22, asterisk) was seen to be completely encapsulated up to the distal end. The capsule was incised (arrow), freeing the

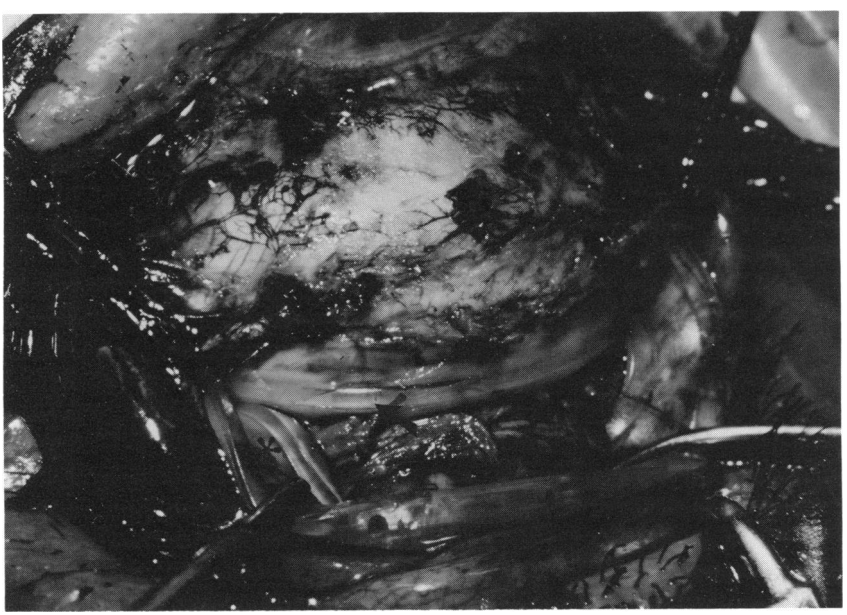


FIGURE 22
An opening (*arrow*) has been made in fibrous capsule enveloping Silastic tube. The 20S band (*asterisk*) is seen overlying tube.

Silastic tube that was firmly adherent to the sclera due to the encapsulation. The Silastic tube was carefully reapproximated with multiple Supramid sutures to appose the encircling band. The walls of the tube were removed for the last 2 mm, and the tongue of Silastic was sutured to the encircling silicone band. The revision resulted in a return to excellent IOP control (IOP $\leq$ 20 mm Hg) without the use of hypotensive agents. Other revisions have revealed the distal Silastic tube to be encapsulated; the tube end extended 5 to 10 mm distal to the last suture allowing the tube to drop out of the silicone gutter onto the episclera, which encapsulated it. In another case, the end was allowed to exit from the gutter and onto the episclera adjacent to the silicone band, where it was encapsulated.

Histopathology

A 60-year-old man with diabetes had a cataract extraction complicated by vitreous loss. An anterior chamber intraocular lens was inserted and, 6 months postoperatively, he developed a fulminant neovascular glaucoma in a light-perception eye. The ACTSEB procedure was successfully performed, with good IOP control 5 months postoperatively. Recurrent

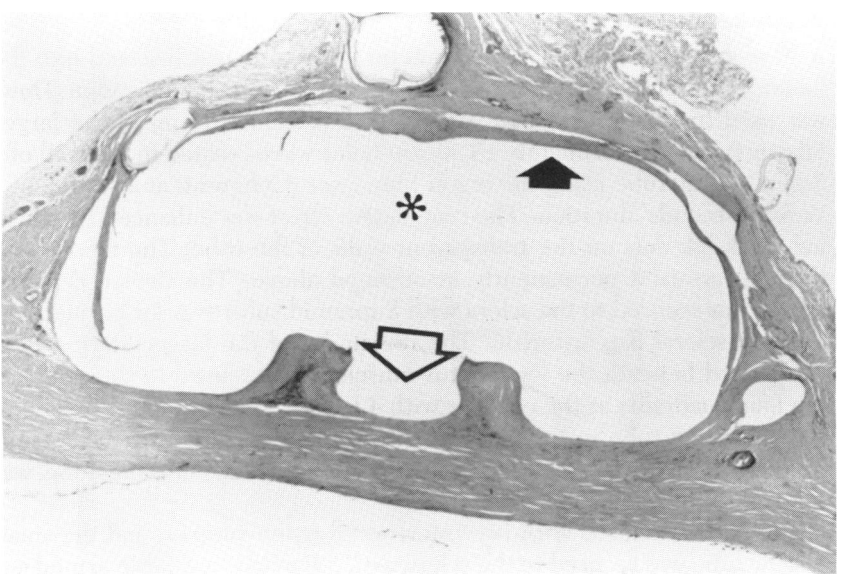


FIGURE 23
Capsule (*solid arrow*) surrounds space (*asterisk*) formerly occupied by silicone band. Silastic tube, displaced by sectioning (*open arrow*), is outlined by two fibrous connective tissue columns arising from episclera with inflammatory cells near their base.

hemorrhage from the rubeosis iridis diabetica caused sufficient discomfort for the patient to request enucleation despite normal IOP. The capsule (Fig 23, solid arrow) surrounding the silicone band (displaced by sectioning) is clearly visible. Two connective tissue columns arising from the episclera, with inflammatory cells near their base, are situated beneath the silicone gutter location. The space (open arrow) between the columns was occupied by the Silastic tube. The connective tissue columns failed to encapsulate the Silastic tube because of the inhibitory effect of the overlying silicone band. The asterisk denotes the approximate location of Silastic tube fixation to the silicone-rubber band.

A NEW DEVICE: AN APPROACH TO AN IDEAL

The animal experiments described earlier revealed that fibrous connective tissue surrounding a Silastic tube will not invade holes of 50 μm or less diameter but merely bridges over the lumen, whereas larger holes (100 μm or greater) are invaded by connective tissue ingrowth. Animal studies also indicated that a thinner capsule is formed around a heparinized implant.

MATERIALS AND METHODS

A 40-mm Silastic tube (outside diameter, 0.62 mm) was inserted into the lumen of a 2-mm Silastic tube for a length of 20 mm. Silicone glue (Dow) was used to secure the small tube to the proximal 5 mm of the larger Silastic tube. Approximately 15 50-μm holes were created in the wall of a 2-mm Silastic tube using the argon blue laser (Coherent) at a setting of 3 W for 2 seconds' duration. The coagulation effect was enhanced by marking black ink dots on the transparent walls of the tube. The device was then heparinized permanently as outlined above. The device (Fig 24, arrow) was secured to the sclera with Supramid sutures prior to raising of a limbal scleral flap (asterisk). The remainder of the larger Silastic tube was passed beneath the four rectus muscles and secured to the sclera in the four quadrants at the equator with 4-0 Supramid sutures. The end of the encircling tube was closed with a 5-0 plain catgut suture a few millimeters from the distal end of the large tube. The Silastic tube was inserted into the anterior chamber.

The flap was closed with two interrupted nylon sutures, and the small Silastic tube was secured to the sclera with 8-0 nylon. A double-armed 4-0 catgut suture was placed beneath the small Silastic tube and brought out through Tenon's and conjunctiva, closing the small Silastic tube. The Tenon's was closed superiorly with 6-0 plain catgut, and the conjunctiva

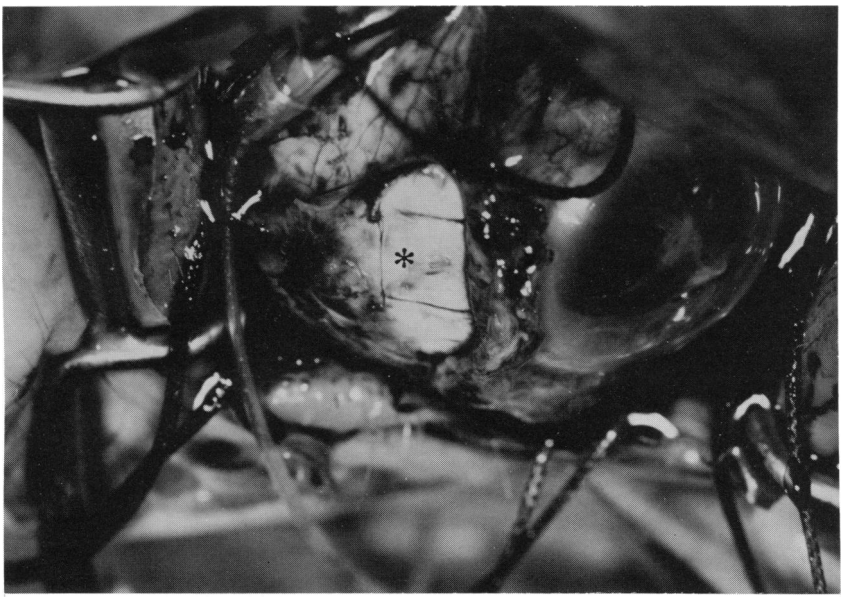


FIGURE 24
Shunt device is secured to sclera (*arrow*) by Supramid sutures prior to placement beneath limbal scleral flap (*asterisk*).

was closed 360° with continuous 5-0 catgut. Antibiotics were instilled and the eye patched.

RESULTS

The device described above has been inserted in five eyes; no significant inflammatory findings were noted postoperatively. The anterior chamber was fully formed on the first day, and IOP ranged between 12 and 18 mm Hg on the first postoperative day. When the tension rose beyond 25 mm Hg between the second and third week, the suture closing the Silastic tube was removed and tension returned to below 20 mm Hg in 5 days. The patients were followed for 3 months and, in all cases, IOP has remained below 20 mm Hg without antiglaucomatous medications.

DISCUSSION

HISTORY

Seton surgery was initiated by Rollet's prophetic prediction in 1907 that the use of a wick to drain a hypopyon ulcer might be applicable to the

treatment of glaucoma. With the exception of Vail's[35] and Weeker's[36] bold trial of draining the vitreous into the posterior subconjunctival space, ophthalmic surgeons selected the limbal area for seton surgery. The first materials to be used as wicks included silk and horsehair.[1-3] Since these materials elicited considerable inflammation, relatively inert metals such as gold,[7] platinum,[10] and tantalum[18] were later used. These materials were too rigid and either eroded through the thin limbal conjunctiva or were displaced anteriorly into the anterior chamber or posteriorly into the subconjunctival space. Thinking that greater stability would improve the results of seton surgery, many of these same materials were placed in cyclodialysis clefts. Although use of this location corrected the dislocation problems, subconjunctival scarring still limited the success of seton surgery.

As a by-product of World War II, synthetic materials became available for medical use. Airmen in the Royal Air Force suffered embedded Perspex corneal foreign bodies, which were tolerated extremely well. Qadeer,[11] noting the success with polymethylmethacrylate as intraocular lens material, began using the same material as a seton. Similarly, silicones used in the American aircraft industry became available for use as biologic materials. Despite the improved tissue tolerance of the new synthetic materials, complications of erosion and subconjunctival fibrosis with plugging of setons persisted. Attempts to solve the complication of hypotony, seen after successful seton surgery, included using a unidirectional valve and allowing the implant to be encapsulated by fibrous tissue before exposing it to aqueous outflow. Schocket's[46,47] ACTSEB procedure uses the gutter of an encircling band as a reservoir for aqueous, which presumably then permeates through the capsule into the orbit. Since the capsule is relatively avascular and retards egress of fluids both from the ACTSEB implant and Molteno's[37-41] orbital plates, improvement of the volume of aqueous that can be handled by the capsule has been obtained by increasing the surface area of implants.

FUNCTION OF THE ACTSEB

HRP was used as a tracer to detect the pathway of aqueous outflow through the capsule surrounding the silicone-rubber encircling band and into the orbit. Seen in large concentration within the space between the 20S band and its enveloping capsule, HRP could then be traced through the collagen lamellae of the wall of the capsule into the orbital tissue. In gross sections, the location of the HRP-reaction product was seen to extend from orbital tissue overlying the 20S band posteriorly to the orbital apex. No significant concentration of HRP was seen in the area

from the limbus of the cornea to the encircling band. Light microscopic sections revealed HRP diffusely infiltrating orbital tissues with high concentrations around orbital vessels. Electron microscopy revealed HRP within the endothelium and lumen of the orbital vessels. Thus the HRP study dramatically demonstrates that aqueous permeates posteriorly and is absorbed by the orbital vessels.

The CT scan study revealed flow through the tube into the reservoir between the capsule of 20S silicone band. Diffusion of the dye into the orbit was not observed since we were unable to obtain a late study and, in addition, the viscous dye material is probably unable to penetrate through the capsule.

The amount of aqueous outflow that permeates the capsule cannot be determined by the HRP or the rabbit CT studies and must await future perfusion or radioisotopic studies.

SILICONE IMPLANTS AND THE FIBROUS TISSUE ENCAPSULATION PHENOMENON

The successful development of a silicone-elastomer hydrocephalus shunt in 1955 heralded the era of silicone implants and prompted a flurry of enthusiastic application of the material to other medical fields, including plastic and reconstructive surgery, orthopedic surgery, and ophthalmology.[54]

This extensive clinical experience with silicone implants has been complemented by exhaustive in vitro toxicity testing, and silicone has often been referred to as an inert material.[54] The term "inert" should be qualified, however, Silicone implants do not cause tissue necrosis when used in vivo or cytotoxicity when tested in vitro, but it is well known that implanted silicone materials within 2 weeks become surrounded by a fibrous capsule separating the implant from the host tissue, a capsule that is contiguous with the tissue but not adherent to the implant.[64] The capsule is composed primarily of fibroblasts and chronic inflammatory cells in a matrix of collagen and glycosaminoglycans and is apparently an attempt to destroy or isolate what the host tissue recognizes to be a foreign body.[65]

The mechanism by which the host tissue recognizes the silicone implant as a foreign body remains largely obscure. There seems to be little doubt, however, that the macrophage plays a central role in this recognition. This is supported by several reports of a monolayer of macrophages or foreign-body giant cells, or both, between the silicone implant and its emveloping fibrous tissue. Studies of these macrophages with electron microscopy and roentgen-ray energy spectrography indicate that the cells are processing a silicon-containing complex that functions as an antigen.

Macrophage migration-inhibition studies seem to indicate that the recognition is a cellular immune phenomenon.[66]

The identity of the proposed silicon-containing complex is not known. One possibility is that silica (SiO_2), a known tissue irritant that is present in silicone rubbers as a filler, is released into the surrounding tissue, where it stimulates the inflammatory response.[66-68] Another hypothesis is that microparticles of silicone function as haptens and become associated with proteins to form an antigenic complex. Yet another intriguing possibility is that macrophages attacking the silicone implant become activated to produce the superoxide anion (O_2^-), a product of the hexose monophosphate pathway, and that this powerful free radical oxidizes the silicone polymer to silica, a biologic irritant.[66]

The macrophage is not only responsible for host-tissue recognition of the silicone implant, but is also implicated as the cellular element that transmits the information to other cell types found in the fibrous capsule.[69,70] It does this through the production of monokines, soluble mediators that regulate the production of hormone-like factors (cytokines) by other cell types, including fibroblasts, lymphocytes, and monocytes. Cytokine effects on target cells include differentiation, proliferation, mobility, and activation.[71] Stimulation of fibroblasts to produce collagen and glycosaminoglycans contributes to the formation of the familiar fibrous capsule.

In vitro studies of sclera-episclera-derived fibroblast-cell lines and silicone implants reported here indicate that fibroblasts attach and proliferate poorly on silicone substrates.

Fibroblasts are known to attach best to two kinds of materials. One category includes the so-called high surface-energy materials, characterized by absolutely smooth, scrupulously clean surfaces. When implants made of such high surface-energy materials (specifically chromium and germanium) were placed into the subdermal fascial plane of rabbits, allowed to heal for 10 to 20 days, and analyzed by standard histopathologic techniques, fibroblasts were found to be attached to the metals by tenacious protein bonds that were difficult to break. In contrast, the lower surface-energy materials (including silicone) implanted into rabbits became "walled-off" by the typical cell-poor, nonadhesive capsule.[72]

In the second category of materials to which fibroblasts readily attach are those that are more bioreactive, that is, less inert. It has been known for some time that collagen substrates encourage fastidious cell types to attach in tissue culture.[73-75] Another cell product important to the phenomenon of cell-substrate adhesion is fibronectin. Coating bioglass with human fibronectin reduces the time required for attachment and changes

the morphology of the attached fibroblasts to extremely flattened, the shape known to be best suited for strong cell-substrate binding.[76]

Medical-grade silicone rubber is neither a high surface-energy material nor a bioreactive one, and the failure of the implanted silicone to become camouflaged by an adherent lining of fibroblasts and their cellular products presumably exposes the naked silicone to the surrounding tissue and results in the inflammatory response central to the development of the enveloping fibrous capsule.

While the fibrous encapsulation of the 20S silicone strip is essential for the success of the ACTSEB procedure, limiting the density of the capsule wall would be a desirable accomplishment, since this would allow less restricted movement of aqueous fluid out of the encircling reservoir and into the orbit. Creating a more bioreactive silicone implant would encourage adherence of fibroblasts to the implant and, according to our postulate, result in a flimsier enveloping capsule.

Soft silicone-rubber prostheses coated with solid collagen and implanted into the subcutaneous tissue of rats are known to result in reduced fibrous-capsule formation.[65] Collagen gel has also been tried as a substrate for the surgical transfer of viable sheets of epithelial cells in the experimental transplantation of ocular surfaces. The obvious problem with collagen-coated implants is that the collagen is itself readily biodegraded; thus, the capsule-reducing qualities of such an implant would only be temporary.[64]

The solution of the problem would be the permanent fixation of the bioreactive molecule to the polymer itself. The Battelle heparinization process[60] results in the physical penetration and fixation of a heparin complex to the silicone polymer. This process is already used on the Silastic-tubing portion of the ACTSEB implant to prevent obstructive blood clots secondary to hyphema.

Heparin is an acid mucopolysaccharide or glycosaminoglycan and is therefore a more bioreactive material than silicone polymer. The Battelle heparinization process has been applied to a 20S silicone strip, which is then incorporated into an ACTSEB implant placed into a rabbit eye. The resulting fibrous capsule is qualitatively less dense than that formed around a plain silicone implant and is much less dense than the capsule induced by the newer Tolentino hydrogel implants.[77] The desired capsular architecture could conceivably be obtained by varying the surface density and character of the silicone-fixed glycosaminoglycan.

CORTICOSTEROID-INDUCED GLAUCOMA IN THE POST-ACTSEB PATIENT: THE POSSIBLE ROLE OF THE FIBROUS CAPSULE

Approximately 15% to 20% of patients develop high responsiveness to corticosteroids between 3 and 5 weeks postoperatively, with IOP increasing from 20 mm Hg to between 25 and 50 mm Hg during this period. This phenomenon is intriguing, for the eyes on which the ACTSEB procedure is to be performed have 360° of peripheral synechiae and, therefore, negligible aqueous outflow through the normal outflow pathways. The new outflow pathway created by the ACTSEB implant and the fibrous capsule that forms by 5 weeks postoperatively may function as an "ectopic trabeculum."

Francois[78] hypothesizes that fibroblasts in the outflow pathway of the eye may be genetically programmed to be sensitive to corticosteroids and thus respond by dramatically increasing their production of glycosaminoglycans and collagen. Consequently, the openings in the trabecular meshwork become smaller as the intercellular ground substance thickens, resulting in an increase in IOP. Autoradiographic studies by Hernandez et al[79] demonstrate nuclear localization of ^{3}H-dexamethasone in scleral fibroblasts adjacent to the outflow pathway and in cells of the trabecular meshwork but not in the nuclei of fibroblasts from the posterior sclera.

These studies support the hypothesis that the ACTSEB implant-induced fibrous capsule is responsible for the corticosteroid responsiveness noted clinically. The capsule is composed primarily of fibroblasts and their cell products, chiefly collagen and glycosaminoglycans. Furthermore, the fibroblasts that form the capsule are probably derived from scleral fibroblasts adjacent to the outflow pathway, cells shown to localize corticosteroids in their nuclei.

Fig 25 is a transmission electron micrograph of a fibrous capsule taken from an enucleated human eye on which the ACTSEB procedure had been performed. A fibroblast is clearly seen to be synthesizing collagen intracellularly.

Preliminary evidence indicates that the fibrous capsule that forms around the implant in patients undergoing the ACTSEB procedure can function as an "ectopic trabeculum" in terms of the targeted response to corticosteroids and the resultant increase in IOP.

Despite the success of the ACTSEB procedure, in eyes with refractory glaucoma, the complications of hyphema and hypotony limit its widespread acceptance.[47] Possible solutions to both problems have been presented. To avoid immediate bleeding secondary to anterior chamber entry through a neovascularizing chamber angle, the wet-field cautery is applied to the needle shaft, which temporarily occludes the perforated

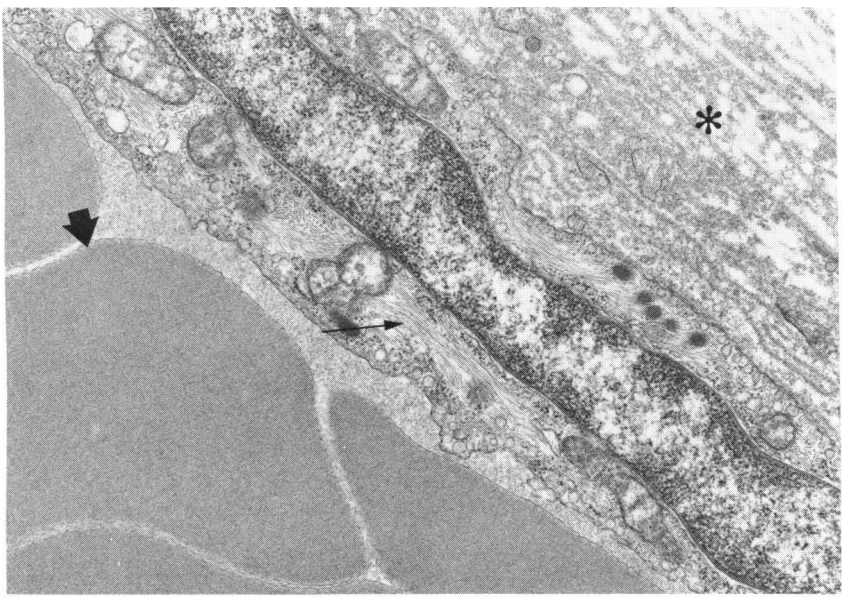


FIGURE 25
Transmission electron micrograph of a fibroblast in fibrous capsule enveloping an ACTSEB implant in an enucleated human eye. Intracellular collagen (*thin arrow*), intercellular matrix (*asterisk*), and capsule surface-adherent red blood cells (*thick arrow*) are seen (× 10,000).

vessels. This technique has dramatically reduced the incidence of intraoperative hyphemas. In order to reduce the possibility of postoperative hyphema obstructing the Silastic tube, a permanent tube-heparinization process has been presented. In experimental tests, heparinized tubes always required no more than the minimum pressure of 10 mm Hg to flush out the clotting blood completely. Hence, the post-ACTSEB IOP of approximately 16 to 20 mm Hg should, in theory, be sufficient to flush out any stasis of blood developing in the Silastic tubes during the postoperative course.

Heparinized tubes, when retested after vigorous rinsing with saline, showed no significant loss in their ability to inhibit obstructive clot formation, and control tubes showed significant deterioration of this ability. This finding not only confirms the conclusion that heparinization decreases tube thrombogenicity, but also implies a stability and permanence to the heparinized tubes in their performance as nonthrombogenic cannulas. The curious finding of increased clotting in the control tube might be explained by residual blood products adhering to the wall despite vigorous washing. Heparinized Silastic tubes were inserted in the

anterior chamber of both rabbits and humans. Increased inflammation was not noted in experimental eyes when compared to controls. Heparinized silicone-rubber materials do not appear to be toxic to the growth of fibroblasts.

These in vitro and in vivo toxicity screenings cannot and should not be viewed as a complete study of the toxicity of biomaterials,[57] but they do seem to exclude a high level of toxicity associated with the heparinized silicone tubing. More in-depth toxicity testing is warranted.

HYPOTONY

Hypotony in the early postoperative period may cause significant complications in the ACTSEB procedure.[46] The hemorrhagic choroidal detachment that may accompany hypotony may then cause vitreous hemorrhage, subretinal fibrosis with visual loss, and phthisis bulbi. The simple solution to the problem of closing the drainage tube in the ACTSEB procedure worked well in five eyes. The capsule surrounding the 20S band has been seen to develop in a rabbit in 1 week and in a human eye in 10 days. Even a minimal capsule provides enough resistance to allow normal IOP. Even without a valve, the successful shunts in Molteno's[37-41] and Schocket's[46,47] procedures give controlled IOP within a narrow range. The risks of suture removal include infection and dislocation of the tube. By continuing to treat the patient with antibiotics for 1 week after suture removal, the risk of infection is minimal. If the tube is well secured to the sclera during the ACTSEB procedure and multiple drops of local anesthetic are instilled, an easy, painless suture removal can be obtained.

TUBE ENCAPSULATION

Tube encapsulation of the orbital end of the Silastic tube is a major cause of ACTSEB failure and occurs whenever the tip separates from the 20S band. This occurs because of nylon suture degradation and therefore, 6-0 Supramid sutures are recommended. The studies presented reveal an inhibition of fibrous connective tissue formation by silicone rubber. In the rabbit eye in which an encircling 20S band was placed against the sclera without scleral securing sutures (a procedure that avoids undue implant pressure), the vascularized episclera seen beneath the gutter of the band disappeared directly under the silicone-rubber column as if a "branding iron" were used (Fig 19A). Similarly, the vascularized mound minimally filled the overlying space in the 20S gutter, suggesting that the invasion of the gutter was aborted by some inhibitory effect from the silicone (Fig 19B). Even the connective tissue capping of Silastic tubes seen in all shunting operations may be considered a manifestation of inhibition.

When one removes the cap of fibrous tissue, aqueous flows freely. The connective tissue does not appear to migrate into and fill the lumen of the silicone tubes. This inhibition by silicone is the primary reason for the success of the ACTSEB procedure.

A NEW DEVICE

A new device (Fig 24), based on the research presented in this thesis, was used successfully in five human eyes. The device substitutes for the 20S band a permanently heparinized 2-mm Silastic tube with 50-μm holes. Our studies reveal that fibrous connective tissue bridges over a 50-μm hole, rather than invading it. This inhibition may be based on an unknown factor that leaches from the silicone rubber, causing a zone of inhibition around the implant. Another explanation may be based on the poor purchase of fibrous connective tissue on the irregular surface of the silicone rubber, as seen by electron microscope (Fig 10). Connective tissue avoidance of small holes is not unique to orbital tissue. Bobyn[58] inserted metal cylinders into adult canine femurs and noted that the metal surface containing 20- to 50-μm pores would not allow ingrowth of fibrous and osseous tissue. Heparinization of the encircling element has been shown to induce a capsule with a loose connective tissue structure having less dense collagen deposition, which would presumably allow a greater volume of aqueous to permeate the capsule (Fig 17). In autopsy studies of filtering blebs of glaucomatous eyes, Addicks[80] an Teng[81] found that a loose connective tissue with minimal collagen deposition correlates well with a successful subconjunctival filtration.

CONCLUSIONS

Aqueous that has been shunted to the reservoir between the encircling silicone-rubber band and its capsule permeates the capsule to be absorbed in orbital vessels. The incidence of bleeding on penetration of the anterior chamber in eyes with neovascular glaucoma can be reduced by cauterization of the needle-perforation tract. The incidence of tube blockage by intraluminal blood clotting can be reduced by the permanent heparinization of the silicone-rubber tubes. Hypotony following the ACTSEB procedure can be eliminated by temporarily closing the Silastic tube with a suture. Silicone rubber remains the best choice for seton material. Although silicone rubber induces the formation of an enveloping capsule, it inhibits connective tissue ingrowth. This inhibition allows the Silastic tube to remain open within the confines of the gutter of the 20S silicone band. The capsule surrounding the silicone band may be

made more permeable to aqueous by the permanent heparinization of the silicone-rubber implant.

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