Macular Surgery

A Clinical Guide

Fabio Patelli
Stanislao Rizzo
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Editors

Springer
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ISBN 978-3-031-63507-6 ISBN 978-3-031-63508-3 (eBook)
https://doi.org/10.1007/978-3-031-63508-3

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Robert Machemer performed the first pars plana vitrectomy in 1970, and within a few years, he and others described peeling membranes from the retina and macula. Since those early days, vitreoretinal surgery has experienced dramatic growth in technology and techniques, with tremendous benefit for patients with sight-threatening retinal conditions.

Since the earliest days of vitreoretinal surgery, preservation of macular function has been paramount. However, modern vitreoretinal surgeons seek not only to preserve but to improve macular function in patients with a continually expanding list of indications.

We have assembled a group of expert and innovative surgeons who provide insights into current state-of-the-art macular surgery. These chapters are an excellent resource for both novice and veteran vitreoretinal surgeons.

Textbooks are necessarily a snapshot in time, so some of what is written in this book may one day be considered quaint, obsolete, or even distressing. If not, our vibrant field will have stagnated!

In describing his first human pars plana vitrectomy, Robert Machemer stated, "This meant the principle worked. *Now* it comes to refinement." We are grateful to the contributors to this book, who are among the many retinal specialists who continue to refine and elevate our field.

Rome, Italy — Stanislao Rizzo
Milan, Italy — Fabio Patelli
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Contents

A Brief History of Macular Surgery

Donald J. D'Amico

Abstract The history of macular surgery is a testament to continuous innovation in ophthalmology, marked by key milestones such as the introduction of pars plana vitrectomy and subsequent advancements in surgical techniques. Innovations like macular hole surgery, internal limiting membrane (ILM) peeling, and the development of membrane dyes have transformed the treatment landscape for various macular pathologies. Despite challenges in addressing conditions like myopic foveoschisis and lamellar macular hole, recent techniques such as the inverted ILM flap have expanded surgical options. Additionally, breakthroughs in electronic retinal prostheses and retinal gene therapy have revolutionized the management of inherited retinal conditions. Looking forward, ongoing research promises further advancements, including retinal transplantation and neuroregeneration, offering hope for improved outcomes and quality of life for patients with macular diseases.

Keywords Macular surgery · Pars plana vitrectomy · Macular hole surgery · Internal limiting membrane (ILM) peeling · Myopic foveoschisis · Lamellar macular hole · Electronic retinal prostheses · Retinal gene therapy · Retinal transplantation · Neuroregeneration

An overview of the remarkable history of macular surgery must begin with a definition. Although macular photocoagulation has been used to improve central vision for many decades, retina surgeons have been reattaching the macula for over a century, and while cataract surgeons have restored vision by reilluminating the macula for centuries more, true macular surgery may be defined as the direct manipulation of the central retina by invasive surgery. Given this definition, the beginning of macular surgery is closely linked to the very introduction of pars plana vitrectomy itself by Dr. Robert Machemer in 1970. The earliest direct manipulation of the macula occurred in the context of his transformative approaches to repair the retinal damage produced

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F. Patelli et al. (eds.), *Macular Surgery*, https://doi.org/10.1007/978-3-031-63508-3_1

by proliferative diabetic retinopathy. This quote (emphasis added) from his seminal 1974 article [1] on two instrument techniques is perhaps the first mention of macular surgery in the literature. "With the removal of the preretinal membrane, all tangential traction on the retina is eliminated. A retina that was detached due to this traction can settle down, and the possibility of future contraction of this membrane is eliminated. **This procedure is especially rewarding when membranes overlying the fovea can be removed. This should have an immediate beneficial effect on the resulting visual acuity."** With those short phrases written a half century ago, preceded by his exacting and extensive experimental work with talented collaborators, macular surgery was born.

In the subsequent rich development of macular surgery, it is easier to identify major innovations and inflexion points than to establish clear credit for the individuals who were responsible for every change. Important presentations at conferences may have remained unpublished with credit awarded to others, literature searches may fail due to foreign language publication or older terminology difficulties, and others may disagree with the priorities selected herein. The author regrets—and sincerely apologizes for—any errors or slights in the attributions and timeline presented. The author will also attribute innovations within the text to the senior author, authors, or acknowledged developers while the corresponding references will be displayed in the reference list with all coauthors in their officially cited author order.

Certain major turning points in macular surgery can be offered that dramatically changed the discipline. Similar to historians dividing earth's history into major geologic time periods in the past such as Jurassic versus Cretaceous, it is possible to offer a timeline of major changes in macular surgery with additional contributions placed in between (Fig. 1). The timeline in this macular surgery specific history intentionally omits many other important developments that advanced vitreoretinal surgery in general such as the introduction of the endolaser, air/fluid exchange, tamponades, and perfluorochemicals, etc.; these general developments certainly aided macular surgery but are beyond the scope of the present review.

Given these parameters, it is possible to identify seven major inflection points in macular surgery: (1) the introduction of vitrectomy with specific macular membrane peeling [1]; (2) macular hole surgery [2]; (3) internal limiting membrane peeling for macular hole [3]; (4) membrane dyes[4, 5]; (5) electronic retinal prosthesis [6]; (6) retinal gene therapy [7]; and (7) ILM flap technique [8]. Within the context of these critical turning points, one can unfold the timeline of innovation in macular surgery.

Following the initial interventions for proliferative diabetic membranes, surgery to remove epiretinal membranes in proliferative vitreoretinopathy (termed "massive periretinal proliferation" at the time) in 1976 [9], and macular pucker in 1977 [10] followed quickly. During these years, there was intensive study of the genesis of the various types of membranes encountered, whether derived from liberated retinal pigment epithelial cells, astrocytes, or fibrocytes in penetrating trauma [11]. Macular surgery in this period primarily consisted of macular pucker removal and macular reattachment/membrane peeling in the context of surgery for proliferative diabetic retinopathy and proliferative vitreoretinopathy. The peeling was performed for years

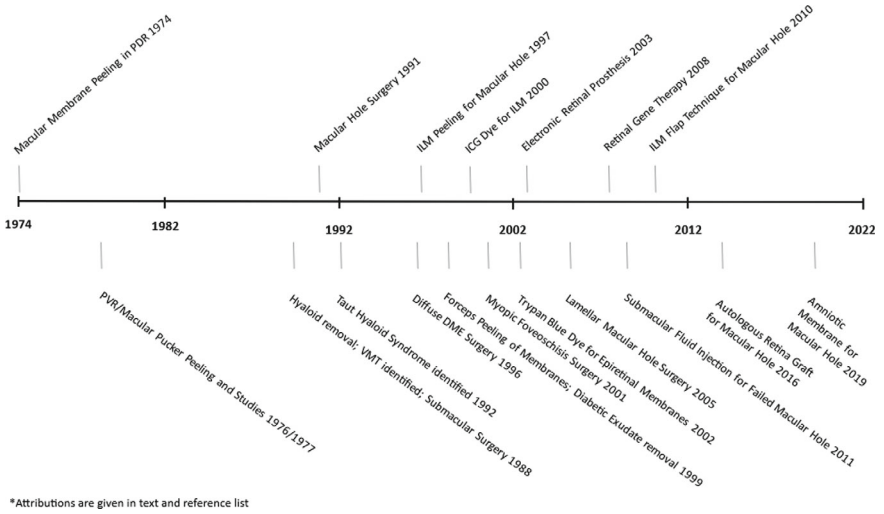

Fig. 1 Timeline of developments in macular surgery*

with bent needles, later specialized membrane pics, and ultimately with forceps after the introduction of "pinch peeling" by Dr. Charles [12].

Three important innovations were introduced in the banner year 1988: (1) the direct surgical elevation and removal of the posterior hyaloid by Drs. Han et al. [13]; (2) the recognition of vitreomacular traction syndrome as a cause of visual loss and the use of vitrectomy as a treatment by Dr. Smiddy [14]; and, perhaps most astonishingly, (3) vitreoretinal surgery to remove submacular hemorrhage and disciform membranes in patients with are-related macular degeneration by Drs. de Juan and Machemer [15].

Posterior hyaloid removal would become a foundational maneuver in vitreoretinal surgery of all types, and numerous techniques and instrument approaches are now available and employed on thousands of cases every year. The identification of vitreomacular traction as a distinct cause of visual loss was a remarkable insight under any circumstances, but in a world before optical coherence tomography, it was nothing less than a triumph; indeed, it brought an entirely new and treatable entity into the field. Subsequent developments would include the use of triamcinolone to better identify vitreous attachments, the injection of intravitreal air to relieve the macular traction, and the use of enzymatic vitreolysis to treat the condition without vitrectomy. Finally, the submacular surgical approaches for hemorrhage and disciform membranes presented are extraordinary for several features. While the subretinal space had previously been approached intentionally in the context of membrane removal in proliferative vitreoretinopathy, foreign body removal, suprachoroidal hemorrhage, and other conditions, the procedures described in 1988 are perhaps the very first time an attached macula was intentionally detached as a distinct maneuver. Later macular surgeries would build on this approach to refine subretinal hemorrhage

and membrane removal, irrigate retained perfluorochemical from the subfoveal area, and most notably, introduce vectors for gene therapy for an ever-increasing array of inherited retinal degenerations.

Although these three innovations energized the field, virtually no one could have been prepared for the supernova event in 1991: the first report of macular hole surgery by Drs. Kelly and Wendel [2]. Their statement of purpose merits repeating: "Our study was a pragmatic, clinical approach toward treating a condition previously considered untreatable." They achieved an anatomic success in 58% of eyes with visual improvement in 42%, taking one of the most hopeless retina conditions and turning it overnight into a successful mainstay of retinal practice. The effectiveness of the initial procedure was subsequently amplified by many additional innovations detailed below, and the pace of innovations around this procedure continues without pause.

The following year, 1992, would bring the identification of taut hyaloid syndrome with macular edema in diabetic retinopathy and demonstration of improvement with vitrectomy and hyaloid removal [16]. Others would later attempt macular surgery for more common forms of diabetic macular edema: Drs. Tachi and Ogino performed hyaloid removal for diffuse diabetic macular edema in 1996 [17], and Dr. Takagi et al. removed hard exudates in 1999 [18]. Although the elimination of taut hyaloid (later identified by Dr. Kaiser et al. as a mini traction retinal detachment [19]) is convincingly joined to visual improvement, the role of surgery for other forms of diabetic macular edema continues to be debated to this day. Modifications have included internal limited membrane peeling, patient selection to enroll patients prior to laser or drug treatment and without chronic features, but the results remain variable and inconclusive. In the face of increasingly successful pharmacotherapy, vitrectomy for diabetic macular edema remains limited or perhaps decreasing in many centers; a much more dramatic decline has already befallen the surgical removal of subretinal neovascular membranes in age-related macular degeneration, also a result of spectacular improvements in drug treatment.

Internal limiting membrane (ILM) peeling has a history that is difficult to ascertain with precision. Dr. Eckardt applied ILM peeling to macular hole surgery in 1997 [3], demonstrating an improvement in closure rates, and this procedure became widespread with the introduction of indocyanine green (ICG) as an ILM stain by Drs. Kadonosono [4] and also by Dr. Burk [5] in 2000. Contributions rapidly followed by Drs. Gandorfer, Kampik, and others in which the potential toxicity of ICG was explored, the alteration of cleavage plane after ICG staining was demonstrated by ultrastructural studies [20], and the multimonth persistence of ICG staining of the optic disc was demonstrated by Dr. Tadayoni [21]. Trypan blue [22] was introduced by Dr. Feron et al. in 2002; other blue dyes introduced subsequently for staining of epiretinal membranes along with ILM (as opposed to ICG which does not stain epiretinal membranes) facilitated their current widespread use in membrane peeling for macular pucker and proliferative vitreoretinopathy. Indeed, the available dyes for vitreoretinal surgery, most recently including lutein, have become a rich palette that permits differential identification of membranes and tissues and facilitates their complete removal.

Macular surgery for myopic foveoschisis and lamellar macular hole, both very common and important conditions, may be considered parallel stories to the developments already mentioned. Drs. Ishikawa and Ogino performed successful vitreoretinal surgery in 2001 for myopic foveoschisis [23], and shortly thereafter, in 2005 Dr. Hirakawa reported successful results in two cases of lamellar macular hole with the use of vitrectomy, ILM peeling, and gas tamponade [24]. Despite these early successes, both conditions remain unpredictable in their outcomes after treatment, and the precise indications for surgery remain unclear to this day. Foveal-sparing ILM or membrane peeling has been recommended for both, and Dr. Shiraga has reported positive results with an ILM inversion technique with embedding of the epiretinal proliferation for repair of lamellar macular holes [25].

Returning to full thickness macular hole, a major innovation was the demonstration of improved closure rates with the use of an inverted ILM flap by Drs. Michalewska (Nawrocka) and Nawrocki in 2010 [8]. The technique was quickly adopted and modified, and the original developers demonstrated that the "taco-like" or folded over temporal flap had equal effectiveness and is now the technique most widely performed [26]. This successes of both ILM peeling and later ILM flap techniques have surprisingly led to several controversies. First, although Dr. Tadayoni demonstrated that ILM peeling is not necessary in surgery for macular holes smaller than 400 microns [27], it is now widely performed in full thickness holes of virtually any size [28]. Second, given the high success with ILM peeling for all macular holes 400 microns or less, most surgeons still peel and discard the ILM for primary cases despite the fact that performing a flap procedure instead would preserve the ILM for use in the rare case that requires reoperation. The first controversy has probably been settled by, unfortunately, ignoring Dr. Tadayoni's data for the smallest macular holes, and the potential negative consequences of unnecessary ILM peeling await further study. The second controversy is only now coming into active discussion and will require additional comparative trials to establish the preferred approach for typical primary cases.

Larger (>400 microns), failed, and recalcitrant macular holes are important categories that have seen numerous innovations for closure, though visual success becomes increasingly uncertain in proportion to macular hole size, duration, and number of unsuccessful interventions. For these difficult cases, Dr. Mahmoud developed an autologous retinal patch technique in 2016 in which a peripheral piece of retina was first delimited by surrounding laser and then slid (most commonly under perfluorochemical) into position under the hole [29]. Later modifications include placement over the retina with maintenance in position by two-week perfluorochemical tamponade. While the anatomic integration of the retinal tissue is impressive and closure of large holes has been demonstrated, the neural functioning of the graft remains conjectural; nevertheless, this work is foundational to several important themes in macular surgery and requires continued careful study.

Realizing the advantages of utilizing a readily available and biocompatible material, submacular insertion of amniotic membrane across the hole was used successfully by Dr. Rizzo et al. [30]. This technique can achieve closure in even the largest holes, though visual results will be progressively limited as the hole size increases.

This innovative approach may also be adapted to macular breaks with retinal detachment in myopia and other difficult situations. Other approaches for failed or difficult macular holes, including stretching the macular tissue by (1) remote subretinal fluid injection by Drs. Oliver and Wojcik [31], or (2) directly injecting viscoelastic across the hole by Dr. Kovacs and D'Amico, have salvaged visual success in mid-large size holes [32], but the largest macular holes (typically greater than 600 or 800 microns) typically require the implantation of a material plug or graft to secure closure.

The final two areas presented in this brief history of macular surgery are so revolutionary they have impact far beyond the confines of the eye. The initial implantation by Dr. Humayun in 2003 with FDA approval in 2103 of the Argus™ II Retinal Prosthesis System offered the first possibility for visual improvement in patients with severe to profound retinitis pigmentosa [6]. This remarkable device was most appropriately lauded for being a breakthrough technology, and a substantial percentage of patients who received the device valued the improvement in visual function it offered. Despite these benefits, difficulties including the need for extensive training to properly interpret the visual signals, the limited and impermanent visual function gained, the exceptionally costly nature of the device, and the failure to develop a financially sustainable model for the company led to its withdrawal from the market in 2020. Other research groups and companies remain highly active with other devices, including epiretinal, subretinal, and cortical, and continued advances in these astonishing technologies may be expected to accompany the parallel progress in microelectronics and vitreoretinal surgery in general. Indeed, though currently unavailable, the Argus™ II program has greatly advanced our understanding of residual retinal function in retinitis pigmentosa, visual processing, and the challenges involved in an electronic neural replacement—the latter two subjects being of great interest to the development of other chip-based prosthetics.

The final area has brought a first in human medicine—the successful, safe, and approved use of gene therapy to treat an inherited condition. The treatment of patients with Leber's congenital amaurosis by Drs. Maguire and Bennett in 2008 is nothing less than a tour de force of focused basic, translational, and clinical research [7]. After carefully targetted basic research, followed by extensive testing in animal models, and culminating in a clinical trial that required construction of a unique "obstacle course" to evaluate the results, the subretinal injection of Luxturna® has restored useful vision to an increasing number of patients. Spurred by this success, a number of gene therapy trials are ongoing for a variety of inherited and non-inherited retinal conditions, and further approvals may be expected. Substantial difficulties in these programs have been encountered: inflammatory responses to injected vectors, difficulty attaining a sufficient dosing for certain desired constructs, areas of retinal pigment epithelial atrophy that appear and enlarge in the months and years following transfection, and others, but the potential of gene therapy is so vast that, similar to the electronic prosthesis, further progress seems assured.

In conclusion, in the short span of fifty years, macular surgery has gone from stripping membranes from the macular surface with a bent needle to embracing the active development of electronic retinal implants while also demonstrating to the world that transformative gene therapy is possible. Thousands of patients benefit

every year from now-routine interventions that did not exist when perhaps one half of currently practicing macular surgeons were born. It is clear that our increasing understanding of macular diseases, coupled with ever more helpful diagnostic tools, will drive continued progress in macular surgery to future refinements and breakthroughs such as partial thickness retinal surgery, true retinal transplantation, retinal revascularization, stem cell replacement therapy, neuroregeneration via biologics or other growth factors, and other approaches as yet unimagined. For the macula, there is certainly much more direct manipulation ahead, and for patients, there will be visual improvement with every innovation.

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History of Dye

Kazuaki Kadonosono

Abstract Dye is an essential element for visualization of structures in the human eye. Vital staining utilized in ophthalmology is one of the most useful examinations to check for any abnormalities, including corneal staining. However, as vitrectomy progressed and began to include the macular region, indocyanine green was used for macular hole surgery by assisting in visualization of the internal limiting membrane (ILM). The ILM has a biochemical composition similar to other basement membranes. A proteomic study demonstrated that collagen IV is the major component of the ILM. Various vital dyes are used to visualize the ILM, and both visualization and toxicity varies depending on the properties of each dye. Digital technology has also recently seen huge progression, enabling surgeons to enhance the ILM with lower concentrations of dye, and even visualize the ILM without additional injections of dye.

Keywords Intravitreal dye · Corneal staining · Vital dyes · Macular hole surgery · Indocyanine green dye · Internal limiting membrane (ILM) · Brilliant blue G · Trypan blue · Triamcinolone

1 Introduction on First Vitrectomy with Vital Dye

1.1 The Era Before Intravitreal Dye

Dye is a crucial element for visualization of structures in the human eye. There are 3 typical methods of injection- general route, vital staining and intra vital staining. Fluorescein angiography (FA) was first used to highlight retinal vessels around 1960 [1–3], using a procedure in which dye was injected intravenously. FA is one of the

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F. Patelli et al. (eds.), *Macular Surgery*, https://doi.org/10.1007/978-3-031-63508-3_2

most important examinations using dye and has been widely adopted in clinics worldwide. Corneal staining [4] is a key method of vital staining utilized in ophthalmology and one of the most useful examinations to check for any abnormalities.

As eye surgery has progressed, there has been increasing interest in methods of improving visualization of transparent eye structures. Research and development of equipment, such as operating microscopes and illumination probes, has allowed surgeons to observe these structures more clearly during surgery. Microscopes have progressed significantly with improved objective lenses, apochromat lenses and contact lenses with surface coatings. Xenon replaced halogen as the primary light source in illumination, allowing for brighter images. However, visualization of the transparent membranes remained elusive to Retinal Surgeons.

The first vitrectomy was done by Machemer for epiretinal membrane in the 1960s [5]. In those days, it was extremely complicated for surgeons to perform vitrectomies, especially macular surgery. We can imagine how challenging the first macular surgery was due to poor visualization, however pioneers must have also been excited at the opportunity of discovering a new therapy.

Macular hole surgery was first performed with separation of the posterior hyaloid membrane and injection of gas in the 1980s. That was a turning point in macular surgery, and it soon gained widespread acceptance among Retinal Surgeons. This innovative surgical technique was performed by two young retinal fellows named Kelly and Wendel [6] based on the pathogenesis of macular hole from Gass's theory [7]. The retina community was enthused at the idea of improving the success rate of macular hole surgery, which was approximately 80% at the time.

About one decade after Gass reported classification of macular holes [7], research on macular hole surgery was performed to look for effective alternatives to posterior hyaloid membrane removal. There was a paper which advocated the importance of the internal limiting membrane in macular hole surgery. Yooh et al. [8] noted that the internal limiting membrane might be an essential element in the treatment of macular holes. This idea was thought to be reasonable based on pathological examinations in which a macular hole was closed by intentionally removing surface tissues, including the ILM, glial cells, and fibrovascular membrane, from around the macular hole.

A small number of Retinal Surgeons who believed in the concept tried to use special instruments such as diamond dusted membrane scrapers to assist in removal of membranes. The diamond-dusted membrane scraper is made from flexible silicone tubing, allowing immature membranes and pigmented cells to be removed from the surface of the retina [9]. Residual cortex vitreous or epiretinal membrane at the edge of a macular hole was thought to be the main cause of macular hole formation, and Retinal Surgeons increasingly came to understand the importance of removing these membranes in macular hole surgery.

However, removal of the ILM without any surgical damage to the retina was still a huge challenge, as the membrane is transparent and can be as thin as 10 μ [10]. Surgeons continued to believe that removal of the perifoveal cortical vitreous, internal limiting membrane, and adherent contractile cells was the best surgical approach to relieving tangential traction and closing idiopathic macula hole and continued

researching surgical approaches to gently removing the internal limiting membrane [11].

2 Internal Limiting Membrane

The internal limiting membrane (ILM) is a vital component of the vitreoretinal interface, exerting a major influence on the development of various eye conditions such as epiretinal membrane (ERM), macular hole, and macular edema [12, 13]. This interface consists of three essential elements: the posterior vitreous cortex, the ILM, and an intervening extracellular matrix. Due to their close interconnection, achieving complete separation is often unfeasible in pathological conditions, leading to complete relief of vitreo-macular traction. Consequently, the standard approach involves the comprehensive removal of the ILM. A profound understanding of the ILM's anatomy is paramount for enhancing the outcomes of ILM removal in macular surgery.

2.1 Biochemical Composition

The ILM has a biochemical composition similar to other basement membranes. The proteomic study demonstrated that collagen IV is the major component of the ILM and the other basement membranes in the eye [14] (Fig. 1).

The origin of the ILM is not clear. The Müller cells are thought to be the major source of ILM proteins, as the ILM is adjacent to the end feet of the Müller cells. It is thought that the ILM proteins are secreted from the lens, ciliary body, and optic disc into the vitreous and then are assembled into the ILM at the retinal surface.

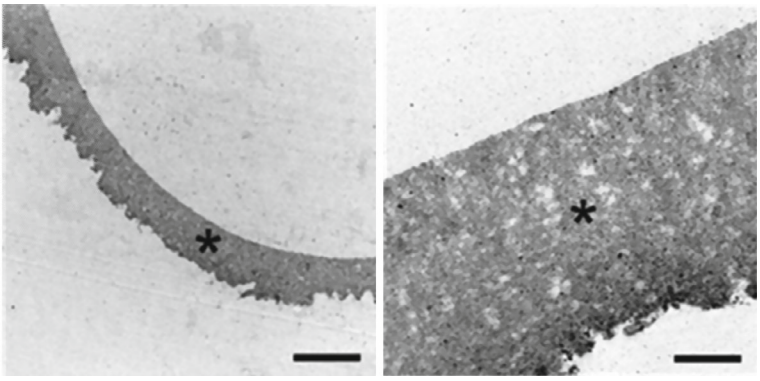

Fig. 1 Transmission electron microscope of ILM. The ILM is 4–10 μ and basement membrane of ILM

There is some debate about whether the ILM regenerates after surgical removal. The expression of the ILM proteins decreased after the developmental process, and most ILM proteins were not detectable in adults [15]. Considering the above findings, ILM regeneration is not likely to occur. No apparent ILM regeneration was noted within 12 months after experimental removal of the ILM using indocyanine green in primate eyes. On the other hand, cultured Müller cells were capable of synthesizing collagen proteins in vitro [16]. Remodeling of the extracellular matrix at the vitreoretinal interface may occur in some pathologic conditions, although the ILM cannot be regenerated completely.

2.2 Role of Internal Limiting Membrane in Macular Surgery

The internal limiting membrane (ILM) plays a key role in the pathogenesis of proliferative diseases, necessitating cell migration, adhesion, and proliferation on the retinal surface. Cell adhesion is facilitated by specific proteins, such as laminin and fibronectin. Interestingly, laminin is primarily situated on the retinal side of the ILM rather than the vitreal side [17]. Furthermore, fibronectin, which is not typically part of the normal ILM composition, is detected in eyes afflicted with conditions like diabetes or proliferative vitreoretinopathy (PVR) [18, 19]. These observations suggest that alterations occur on the vitreal side of the ILM to promote cell adhesion in proliferative conditions, underscoring the importance of removing the pathological ILM to prevent membrane formation. Notably, peeling of the ILM has been reported to reduce postoperative macular pucker following retinal detachment surgery. and to decrease the recurrence of epiretinal membranes (ERM) [20, 21]. In a clinical setting there are advantages including acquired flexibility of the ILM, prevention of reproliferation, and regeneration of muller cells. Drawbacks include damage to ganglion cells, and harm to the neurofiber layer resulting in visual field defects. Intraoperative pictures of ILM removal in macular surgery show a meshwork appearance which does not appear to harm retinal function. These days ILM removal during macular hole surgery has become widely accepted in the retina community.

3 Era of Vital Dye for Vitrectomy

3.1 Safe Use of Indocyanine Green Dye in the Human Body

Indocyanine green (ICG) is a relatively nontoxic Tricarbocyanine dye and has been used in humans for many years [22, 23]. We use ICG dye in angiography examination for macular diseases related to choroidal abnormalities such as PCV, exudative age-related macular degeneration and pachychoroid spectrum since Yannuzzi introduced his unique analysis method of vascularized pigment epithelial detachments using

indocyanine green video angiography [24]. There have been no reports of patients who suffered severe issues such as anaphylactic shock.

The evaluation of hepatic function and functional capacity of the liver are essential tasks in hepatology as well as in hepatobiliary surgery. Indocyanine green (ICG) is a widely applied test compound that is routinely used in clinical settings to evaluate hepatic function. After intravenous administration, ICG is taken up exclusively by the liver and excreted unchanged into the bile [25]. It is not reabsorbed by the intestine and does not undergo enterohepatic circulation. As a result, ICG is an ideal test compound to test hepatic uptake and biliary excretion.

Furthermore, ICG was used to stain the anterior capsule membrane in white mature cataracts [26]. This history of clinical applications of ICG to the human body, and especially the eye, made it a safe and reliable choice for use in retinal surgery.

3.2 Selective Staining of the ILM with ICG

ICG was first used for macular hole surgery in 2000 [27] (Fig. 2). There had been no way for Retinal Surgeons to resolve the issue of visualizing the ILM, until the intraoperative vital dye ICG was first used for idiopathic macular hole surgery, leading to a dramatic change in approaches to macular surgery (Fig. 3).

ILM removal has become an essential procedure in the field because ICG dye can not only visualize the ILM, but negatively visualize other components such as the ERM, and fibrovascular tissues (Fig. 4). This selective staining property of ICG was an essential factor in it becoming widely accepted as a necessary surgical procedure in macular surgery. The ILM consists of collagen IV, along with other basement membrane proteins including the laminin family, nidogen, agrin, perlecan, and collagen XVIII [20]. The ILM has a lower concentration of collagen IV compared to other basement membranes, and the most prominent proteoglycan is perlecan, which is responsible for the high-water content of the ILM [21]. These characteristics are the main reason that ICG can be used to stain the ILM selectively.

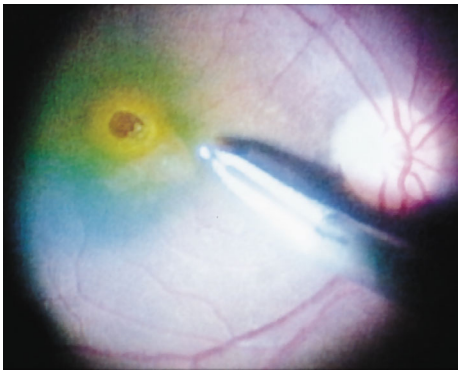

Fig. 2 An intraoperative picture of ILM staining in macular hole surgery from a journal. The first report on ILM peeling with ICG was published in 2000

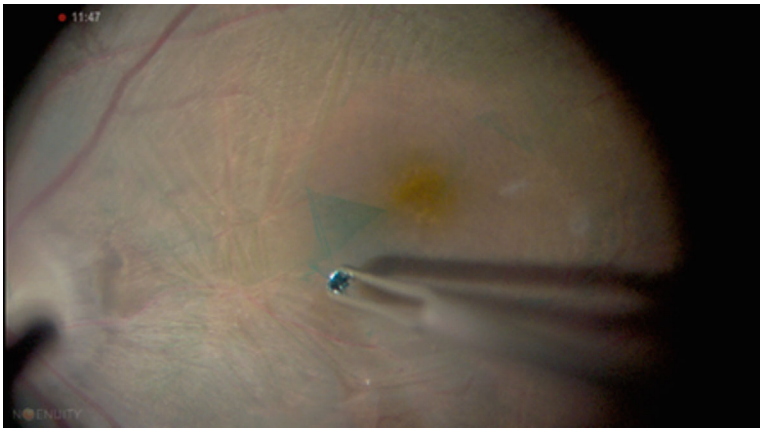

Fig. 3 An intraoperative image of recent surgical technique for ILM peeling with ICG. The concentration of ICG is 0.03% mixed with low molecule weight visco-elastic material

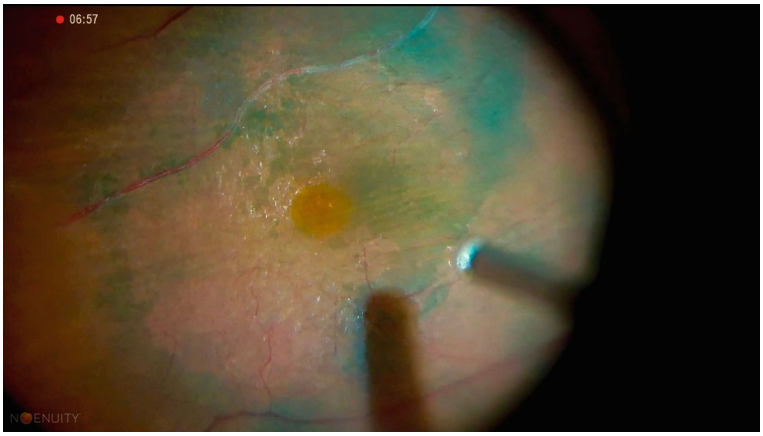

Fig. 4 An intraoperative image of an eye with ERM stained with ICG. Parts both negatively and positively stained with ICG, allow surgeons to identify the location of the ERM

Therefore, ICG which previously could only be utilized through injections into the body for liver examination, was selected as an ideal dye for use in staining the posterior segment. The first report of ILM staining with ICG encouraged Retinal Surgeons to perform macular hole surgery leading to improvements in anatomical and functional results.

3.3 Clinical Setting of Indocyanine Green to Macular Surgery

A procedure of intravitreal indocyanine green that we developed is that 25 mg of ICG was distributed into 10 cc balanced saline solution, and 0.2 cc of which was mixed with viscoelastic material with low molecule. The concentration of that is 0.03% and ICG is unlikely to be dispersed.

There are different methods used for injection of vital dyes from injections into the body, to irradiation using light as a photosensitizer. The shift of absorption wavelength occurs in the absorption spectrum of ICG when albumin is present in solution and the dye is bound to albumin [28]. The similarity of the absorption spectrum of the dye in human plasma and in albumin solution, and the identity of the absorption maxima suggest that plasma proteins other than albumin are not important in the binding of ICG. These data are supported by the results of starch block electrophoresis.

The absorption of light by indocyanine green (ICG) can trigger retinal phototoxicity. While it is commonly understood that ultraviolet and blue light radiation pose risks to the retina, there is also concern that the light emitted by ICG in the range of 780–810 nm wavelength might have a photochemical impact on the retina. Some studies have suggested a potential photosensitizing effect when the stained retina is exposed to intraoperative illumination within the 380–760 nm wavelength range, emitted by commonly used vitrectomy light sources, which could lead to morphological damage in the inner retina. However, it is important to note that these findings have not been consistently confirmed by other investigations. When performing macular surgery with endoillumination that includes longer wavelengths, such as 810 nm, there could be a possibility of irradiation effects on the retina.

Additionally, recent research has focused on assessing retinal light hazards during macular surgery using digital three-dimensional visualization systems (3D) in comparison to conventional microscopes (CM). It has been found that the 3D digitally assisted visualization system offers a significantly safer approach to macular surgery when considering potential retinal hazards.

In in vivo studies, RPE cells were susceptible to damage with high concentrations of ICG and/or longer exposure times. Enaida et al. reported that RPE-19 cells showed significantly decreased survival rates with an exposure time of more than 24 h and at higher concentrations of ICG than the normal range which is between 0.05 and 0.5%. The method of injecting ICG into the vitreous is a key factor in avoiding direct mechanical injury to the RPE cells in a macular hole. These clinical findings changed the clinical settings in which ICG vital dyes were used, leading to safer methods approved by the majority of Surgeons.

4 Other Dyes

4.1 Brilliant Blue G

In the early 2000s several new dyes were researched and developed, and there was some controversy over which vital dye was the best for application to macular surgery. Trypan Blue was introduced to stain the membrane blue; however, it didn't seem to selectively stain the ILM as well as ICG. Brilliant blue G (BBG) was another dye that had been used to stain micro-organs inside cells in the laboratory [29]. According to the first laboratory examination of BBG, it proved to have lower toxicity than other dyes such as ICG and Trypan Blue. Clinical studies of BBG application reported acceptable results without any related issues. As a result, BBG became widely accepted among Retinal Specialists hoping to avoid unexpected complications [30].

BBG was introduced as a surgical adjuvant for chromovitrectomy in 2006 and, this dye was purported to stain the ILM and to have no significant in vivo toxicity. After other dyes such as BBG were introduced, the technique of using vital dye became known as chromovitrectomy.

BBG is more hydro soluble than ICG and IfCG; it would thus penetrate less into the cells and be more easily washed away, leaving less residues after surgery. For this reason, BBG represents a viable alternative to ICG and IfCG in chromovitrectomy due to its suitable affinity for the ILM.

4.2 Trypan Blue

Trypan blue (TB) usage mostly extends to blue dye application for ERM staining [31]. TB exhibits outstanding affinity for the ERM because of the strong presence of dead glial cells within those membranes. I personally use it for immature PVR which may minimize mechanical trauma to the retina during ERM removal and allows me to determine the full extent of the ERM. TB in various doses may enhance the ability to detect both the prolapsed vitreous in the anterior chamber and the posterior vitreous remaining in the vitreous cavity, but it is inferior to triamcinolone acetonide. Regarding the chronic toxicity of TB, it has been reported that it induces arrest of the cell cycle at G0–G1 via increased expression of p21.

4.3 Triamcinolone Acetonide

Triamcinolone acetonide improves visualization as well as other dyes [32]. The crystals of the steroid adhere to the acellular tissue, thereby enabling a clear contrast between the empty vitreous cavity compared to areas with the vitreous fibers

remaining. The surgical technique for TA application consists of a direct injection of the agent into the vitreous cavity toward the area of interest. TA-assisted removal of the internal limiting membrane was used in many cases since the white specks and crystals may deposit over the ILM, thereby facilitating ILM removal. For this reason, some authors suggest that postoperative residual TA could enhance surgical results. Injecting this steroid during vitrectomy for the management of retinal detachment may prevent fibrin reaction and PVR postoperatively. The commonly used formulation of TA, kenalog, is not formulated for the eye, for this reason, there is a risk of pseudoendophthalmitis and retina toxicity when injected intravitreally. There have been reports on the toxicity of TA on retinal pigment epithelial cells (RPE) in vitro whereas ex vivo and in vivo studies have not shown any significant toxicity to the retina.

5 Use of Retinal Vital Dyes and Issues with Toxicity

In the first report on clinical application of ICG, ICG was prepared as a vital dye for macular hole surgery at a concentration of 0.06% ICG mixed with a low molecular weight viscoelastic material [27]. The study reported a success rate of macular hole closure of 82.4% among the 12 eyes studied, and mean visual improvement was 0.34 logMAR (from 20/200 to 20/25) at 6 months postoperatively. In this study there were no eyes with decreased visual acuity, and there were not any intra or postoperative complications such as endophthalmitis, or retinal detachment seen.

After ICG dye application was introduced in macular hole surgery, a number of reports surfaced describing issues related to ICG use such as macular atrophy, disc atrophy and other serious issues [33, 34]. Some pathological examinations with in vivo studies showed that RPE cells were negatively affected by ICG depending on the concentration of dyes exposure time of ICG to the retina and the method of injection [35]. Other experimental studies showed cell damage such as shortened survival time in ganglion cells [36–38]. These findings led to updated techniques for ICG vital dye staining as well as the development of new dyes.

6 Differences in Visualization of Each Dye

Visualization is influenced by several factors such as brightness, color contrast, hue, gamma and saturation, and a good combination of these elements makes it possible to enhance visualization. The color of dyes is a key factor which varies depending on the dye (Fig. 5).

Vital dyes are used to visualize the ILM, and visualization of the ILM varies depending on the property of each dye. In certain conditions, and at safe concentrations, visualization depends heavily on color contrast. Studies indicated that a green color such as ICG can provide higher contrast than either the blue or light blue colors

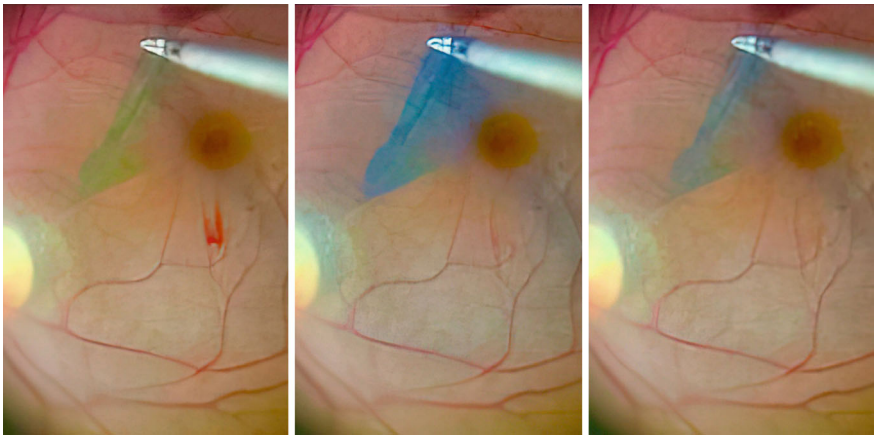

Fig. 5 Images showing differences in visualization between ICG, BBG and Trypan blue. There are clear differences in visibility with different dyes

typically seen with BBG. It has also become apparent that visualization of the ILM changes in Caucasian, Asian and African populations due to differences in choroidal color [39].

In highly myopic eyes displaying macular atrophy, the green color allows us to observe the ILM more clearly than with blue colors, resulting in ICG being more widely used in eyes with myopic traction maculopathy (Fig. 6).

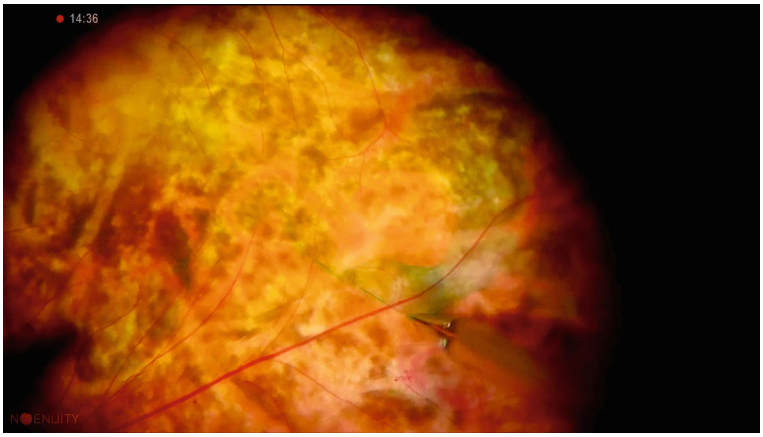

Fig. 6 An intraoperative image of ILM peeling using ICG. The ILM is more clearly stained with ICG than other dyes in a highly myopic eye