

Retinal and Vitreoretinal Diseases and Surgery

Samuel Boyd, MD • Rafael Cortez, MD • Nelson Sabates, MD



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Rafael Cortez, MD
Nelson Sabates, MD





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Phone: (507) 301-0496 / 97 - Fax: (507) 301-0499

E-mail: cservice@jphmedical.com

Worldwide Web: www.jphmedical.com



EDITORS

SAMUEL BOYD, MD

Director, Laser Section, and Associate Director, Retina and Vitreous
Department, Clinica Boyd-
Ophthalmology Center
Panama

RAFAEL CORTEZ, MD

Medical Director and Founder
Centro de Cirugía Oftalmológica
(CECOF),
Caracas, Venezuela

NELSON SABATES, MD

Professor and Chairman,
Department of Ophthalmology,
University of Missouri
Eye Foundation of Kansas City
Kansas City, Missouri, USA



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PREFACE

It is a pleasure to introduce *Retinal and Vitreoretinal Diseases and Surgery* by Samuel Boyd, MD, Rafael Cortez, MD and Nelson Sabates, MD. This volume contains chapters written by global leaders in the field, and has both breadth and depth in covering clinically relevant and important topics. In forty-one chapters the editors have selected authors with particular areas of expertise, and areas of interest not only to vitreoretinal surgeons, but also to medical retina specialists, comprehensivists and trainees.

With 718 pages of content and 1000 color images and illustrations this book provides not only the fundamentals but the focus needed for the clinician to care for patients with both straightforward and complex retinal disease.

Joel S. Schuman, MD.
Professor and Chairman,
Department of Ophthalmology
University of Pittsburgh School of Medicine.
Director, UPMC Eye Center Professor of Bioengineering
Pittsburgh, PA



CONTRIBUTING AUTHORS

Carlos A. Abdala, MD

Retina Specialist,
Ophthalmology Center
Unidad Laser del Atlantico
Barranquilla, Colombia

Pedro Amat-Peral, MD

Alicante Institute of Ophthalmology,
VISSUM, Retina Unit,
Alicante, Spain

J. Fernando Arevalo, MD, FACS

Director,
Clinica Oftalmologica Centro Caracas
The Arevalo-Coutinho Foundation for
Research in Ophthalmology
Caracas, Venezuela

Enrique Ariza Camacho, MD

Unidad Oftalmológica del Valle
Mexico D.F., Mexico

George K. Asdourian, MD

Professor of Ophthalmology
University of Massachusetts,
School of Medicine
Worcester, Massachusetts

Maria H. Berrocal, MD

Berrocal and Associates
Assistant Professor
University of Puerto Rico
San Juan, Puerto Rico

Samuel Boyd, MD

Director, Laser Section, and Associate
Director, Retina and Vitreous
Department, Clinica Boyd-
Ophthalmology Center
Panama

Rosario Brancato, MD

Professor and Chairman
Department of Ophthalmology and
Visual Sciences
University Hospital San Raffaele
Milano, Italy

Dhiren Bujarborua, MD

Director, Pragjyoti Eye Care and
Research Centre,
Guwahati, India

Jorge I. Calzada, MD

Vitreo-Retinal Surgery,
Chief of Retinopathy of Prematurity
Service, Charles Retina Institute.
Assistant Clinical Professor
Hamilton Eye Institute
University of Tennessee
Memphis, TN, USA

Stanley Chang, MD

Columbia University of
Physicians and Surgeons
Department Ophthalmology
New York, NY, USA

**Steve Charles, MD**

Director,
Charles Retina Institute
Memphis, Tennessee, USA

Borja Corcóstegui, MD.

Professor of Ophthalmology.
Instituto de Microcirugía Ocular (IMO).
Barcelona, Spain

Rafael T. Cortez, MD

Medical Director and Founder
Centro de Cirugía Oftalmológica
(CECOF),
Caracas, Venezuela

Emanuele Di Bartolo, MD

Ospedale Santa Chiara di Pisa
Italy

Francesco Faraldi, MD

Ospedale Oftalmico di Torino
Italy

Marta Fernández-Muñoz, MD, PhD

Pío del Río Hortega University
Hospital, Ophthalmology Unit,
Valladolid, Spain

Anibal Martin Folgar, MD

Laboratory of Investigations in
Ophthalmology and Visual Sciences
LIOCIV
Department of Pathology
University of Buenos Aires
Buenos Aires, Argentina

Gerardo García-Aguirre, MD

Retina Service
Hospital "Dr. Luis Sánchez Bulnes"
Asociación para Evitar la Ceguera
Mexico, DF, Mexico.
Clinical Professor of Ophthalmology
School of Medicine - Tecnológico de
Monterrey
Mexico, DF, Mexico

Justus G. Garweg, MD

Berner Augenklinik am Lindenhofspital
Swiss Eye Institute,
University of Bern,
Bern, Switzerland

Gian Paolo Giuliari, MD.

Princess Margaret Hospital
Ocular Oncology Department
Toronto, Ontario
Canada

Federico A. Graue-Wiechers, MD

Chief, Vitreoretinal Department
Instituto de Oftalmología Conde de
Valenciana
Mexico, D.F.

Prof. Patrick C.P. Ho, MD

Clinical Professor of Ophthalmology,
Chinese Academy of Traditional
Medicine and Eye Hospital
Beijing, China
Hong Kong's former Secretary for
Home Affairs,
Regional Chair Person for the
International Association
for the Prevention of Blindness
Beijing, China

***Shalesh Kaushal, MD., Ph.D.***

Associate Professor and Chairman
Department of Ophthalmology
University of Massachusetts Memorial
Medical Center
Worcester, Massachusetts, USA

Ferenc Kuhn, MD., PhD

President, American Society of
Ocular Trauma
Executive Vice President, International
Society of Ocular Trauma
Associate Professor of Clinical
Ophthalmology,
University of Alabama at Birmingham.
Associate Director of Clinical Research,
Helen Keller Foundation for Research
and Education
Birmingham, Alabama, USA

Madhavi Kurli, MD

The New York Eye and Ear Infirmary,
New York, USA

Ketan Laud, MD

New York University School of
Medicine
New York, New York, USA

Janice C. Law, MD

Assistant Professor
Vitreoretinal Surgery and Diseases
Department of Ophthalmology
and Visual Sciences
Vanderbilt Eye Institute
Nashville, Tennessee, USA

Konstantinidis Lazaros, MD

Hôpital Ophtalmique Jules Gonin,
University of Lausanne,
Switzerland

Hilel Lewis, MD

Department of Ophthalmology,
Edward S. Harkness Eye Institute,
Columbia University College of
Physicians and Surgeons,
New York, New York, USA

Jeffrey K. Luttrull, MD

Director
Retina Diagnostic Laboratory
Ventura County Retina Vitreous
Medical Group
Ventura, California

Sachin Mehta, MD

Department of Ophthalmology and
Visual Sciences,
Vanderbilt Eye Institute,
Vanderbilt University School of
Medicine,
Nashville, Tennessee, USA

Javier A. Montero, MD, PhD

Pío del Río Hortega University
Hospital, Ophthalmology Unit,
Valladolid, Spain.
Alicante Institute of Ophthalmology,
VISSUM, Retina Unit,
Alicante, Spain

Virgilio Morales-Cantón, MD

Chief, Retina Service
Asociación para Evitar la Ceguera
en Mexico
Mexico DF, Mexico

**Robert Morris, MD**

President, International Society of
Ocular Trauma
Founder, United States Eye Injury
Registry
President, Helen Keller Foundation
Associate Professor of Clinical
Ophthalmology,
University of Alabama at Birmingham
Birmingham, Alabama, USA

Darius Moshfeghi, MD

Associate Professor of Ophthalmology
Stanford University
Palo Alto, California, USA

Manish Nagpal, MD

Retina Foundation
Gujarat, India

P. N. Nagpal, MD

Director,
RETINA FOUNDATION
Aso-Palov Eye Hospital
Ahmedabad, India

Yoshihide Nakai, MD

Tokai Eye Clinic
Tokai University School of Medicine
Hadokoro-cho Tsu Mie, Japan

Shunsuke Osawa, MD

Okanami General Hospital,
Iga, Japan

Anil Patil, MD

Vitreo Retinal Consultant,
Retina Foundation
Ahmedabad, India

David E. Pelayes, MD., PhD.

Professor of Ophthalmology,
University of Buenos Aires.
Coordinator,
Laboratory of Investigations in
Ophthalmology and Visual Sciences
LIOCIV
University of Buenos Aires
Buenos Aires, Argentina

Ana T. Peralta, MD

Ophthalmologist,
Ophthalmology Center
Unidad Laser del Atlantico
Barranquilla, Colombia

George B. Peters III, MD., M.B.A.

Assistant Professor of Ophthalmology
University of Massachusetts, School of
Medicine
Worcester, Massachusetts, USA

Gholam Peyman, MD

Professor of Ophthalmology
Co-Director of Vitreo-Retinal Surgery
Tulane University Health Sciences
Center, School of Medicine
Department of Ophthalmology
New Orleans, Louisiana, USA

L. Pierro, MD

Department of Ophthalmology
and Visual Sciences
University Hospital San Raffaele
Milano, Italy



Hugo Quiroz-Mercado, MD
Chief, Retina Service
Asociacion Para Evitar la Ceguera in
Mexico, (APEC),
Chief, Experimental Surgery Laboratory,
APEC,
Professor of Ophthalmology
Universidad Nacional de Autonoma
de Mexico (UNAM)
Mexico, DF., Mexico

Maria Maddalena Rabbione, MD
Ospedale Oftalmico di Torino
Italy

Franco M. Recchia, MD
Department of Ophthalmology and Vi-
sual Sciences, Vanderbilt Eye Institute,
Vanderbilt University School of
Medicine,
Nashville, Tennessee, USA

Carl D. Regillo, MD, FACS
Director, Clinical Retina Research
Wills Eye Institute
Professor of Ophthalmology
Thomas Jefferson University
Philadelphia, PA, USA

Stanislao Rizzo, MD
Chair U.O.Chirurgia Oftalmica
Azienda Ospedaliero Universitaria
Pisana
Pisa, Italy

Elena Rodríguez-Neila MD
Instituto de Microcirugía Ocular (IMO).
Barcelona, Spain

**Richard B. Rosen, MD, FACS, FASRS.,
CRA.**
Vice Chair and Surgeon Director
Director of Ophthalmology Research
New York Eye and Ear Infirmary
Professor of Ophthalmology
New York Medical College
New York, New York, USA

Kamolika Roy, MD
Department of Ophthalmology,
University of Massachusetts Medical
School, Department of Ophthalmology,
Worcester, MA, USA

Jose M. Ruiz-Moreno, MD, PhD
Alicante Institute of Ophthalmology,
VISSUM, Retina Unit,
Alicante, Spain
Albacete Medical School,
Castilla La Mancha University,
Spain

Felix Sabates, MD
Professor,
Department of Ophthalmology,
University of Missouri
Eye Foundation of Kansas City
Kansas City, Missouri, USA

Nelson Sabates, MD
Professor and Chairman,
Department of Ophthalmology,
University of Missouri
Eye Foundation of Kansas City
Kansas City, Missouri, USA



Natalia Saldaña-Verduzco, MD
Autonomous University of Mexico
Vitreous Retinal Department,
Institute of Ophthalmology
Fundación Conde de Valenciana
Mexico, D.F.

Jason S. Slakter, MD
Clinical Professor of Ophthalmology
New York University School of
Medicine;
Surgeon Director,
Manhattan Eye, Ear & Throat Hospital
New York, New York, USA

Marc Spirn, MD
Instructor of Ophthalmology
Wills Eye Institute
Thomas Jefferson University
Philadelphia, PA, USA

Linda Stein, MS
Science Writer
Department of Ophthalmology
University of Massachusetts,
School of Medicine
Worcester, Massachusetts, USA

Paul Sternberg, Jr., MD
Professor and Chairman
Department of Ophthalmology
and Visual Sciences,
Vanderbilt Eye Institute, Vanderbilt
University School of Medicine,
Nashville, Tennessee, USA

Savak Teymoorian, MD., MBA
Resident Physician,
Department of Ophthalmology,
University of Missouri
Eye Foundation of Kansas City
Kansas City, Missouri, USA

Juan Verdaguer T., MD
Professor of Ophthalmology,
University of Chile and
University of Los Andes.
Academic Director,
Fundación Oftalmológica Los Andes
Santiago, Chile

Juan Ignacio Verdaguer D., MD
Associate Professor of Ophthalmology,
University of Los Andes
Santiago, Chile

C. Douglas Witherspoon, MD., FACS.
Professor of Ophthalmology,
University of Alabama
Birmingham, Alabama, USA

Lihteh Wu, MD
Instituto de Cirugía Ocular
San José, Costa Rica

Jiong Yan, MD
Assistant Professor
Vitreous-Retina Division
Emory Eye Center
Atlanta, Georgia, USA

Jorge O. Zarate, MD., PhD.
Professor of Pathology
University of Buenos Aires
Director of the Laboratory of
Investigations in Ophthalmology
and Visual Sciences LIOCiV
Department of Pathology
University of Buenos Aires
Buenos Aires, Argentina

Leonidas Zografos, MD
Hôpital Ophtalmique Jules Gonin,
University of Lausanne,
Switzerland



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<i>Jorge O. Zarate, MD, PhD</i>	

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<i>Borja Corcóstegui, MD</i>	

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<i>Anil Patil, MD</i>	

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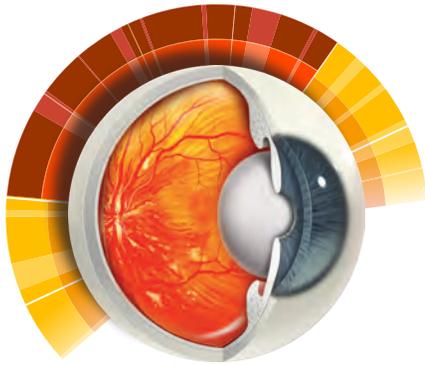
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Section 1

Diagnostic Systems in Retina



1

The Normal Retina

SAMUEL BOYD, MD

In vertebrate embryonic development, the retina and the optic nerve originate as outgrowths of the developing brain, so the retina is considered part of the central nervous system (CNS). It is the only part of the CNS that can be imaged directly.

The retina ranges in thickness from about 100-500 μm . It is a composite of numerous cellular and synaptic layers which can be grossly split into an outer epithelial layer (referred to as the retinal epithelium or retinal pigment epithelium) and an inner sensory layer (referred to as the sensory retina or neuroretina). The retina is one of the most metabolically active tissues in the body. Its major function is to convert light energy into chemical and electrical energy so that vision can occur (if a functional brain is present).

The retina is a complex, layered structure with several layers of neurons intercon-

nected by synapses. The only neurons that are directly sensitive to light are the photoreceptor cells. These are mainly of two types: the rods and cones. Rods function mainly in dim light, while cones support daytime vision. A third, much rarer type of photoreceptor, the photosensitive ganglion cell, is important for reflexive responses to bright daylight.

Neural signals from the rods and cones undergo complex processing by other neurons of the retina. The output takes the form of action potentials in retinal ganglion cells whose axons form the optic nerve. Several important features of visual perception can be traced to the retinal encoding and processing of light.

Functional Anatomy

The vital structures of the retina are conveniently arranged for us in distinct



layers. These are clearly shown in Figure 1. The order of retinal layers starting from outer to inner layers (that is, from choroid to vitreous) is as follows: Retinal pigment epithelium, Photoreceptor outer segments, Photoreceptor inner segments, Outer or external limiting membrane, Outer or external nuclear layer, Outer or external plexiform layer, Inner nuclear layer, Inner plexiform layer, Ganglion cell layer, Nerve fiber layer, Internal limiting membrane.

The outermost layers next to the choriocapillaris are Bruch's membrane and the retinal pigment epithelium (RPE). Bruch's membrane allows passage of nutrients from the choriocapillaris to the retina, while acting as a barrier to invasion of the retina by its vessels. The RPE are supporting cells for the neural portion of the retina and are important for photopigment regeneration. The RPE is dark with melanin, which decreases light scatter within the eye. The rod and cone layer contains the outer and inner segments of the rods and cones photoreceptors. The outer limiting membrane orders these from the outer nuclear layer (ONL) - the cell bodies of rods and cones. Next, we see the outer plexiform layer (OPL), with the rods and cones axons horizontal cell dendrites, and bipolar dendrites. The inner nuclear layer (INL) contains the nuclei of the horizontal and bipolar cells. The inner plexiform layer (IPL) neatly contains the axons of the bipolar cells (the amacrine), and the dendrites of the ganglion cells. The layer of ganglion cells (GCL), is covered by the layer of the optic nerve fibers - fibers from ganglion cells traversing the retina to leave the eyeball at

the optic disk. Finally, the internal limiting membrane forms the border between the retina and the vitreous.

There are two distinct vascular systems in the ocular fundus: retinal and choroidal. The retinal vasculature is identified in Figure 1C as (U) and (V). The choroidal vasculature is identified in Figure 1C as W. Between them lies the retinal pigment epithelium (RPE), Fig. 1-C-X, an opaque monolayer of cells anterior to the choroid that normally largely obscures its vasculature from ophthalmoscopic view. Pathologic alteration of the structure and pigmentation of the RPE affects the pattern of choroidal fluorescence perceptible during angiographic studies. Familiarity with the anatomy and interaction of these anatomic layers is the key to accurate interpretation of fluorescein angiograms, an examination which is vital to the diagnosis of retinal diseases.

The photoreceptor cells (rods and cones), Figure 1C-K and T, are supplied with nutrients from the choroid (Figure 1C-W) through the retinal pigment epithelium (Figure 1C-X).

Choroid

The choroid is composed of connective tissue and vessels that nourish the RPE (Figure 1C-X) and outer retina (Figure 1C-H). The inner layer is the choriocapillaris (Figure 1C-Y). The choroidal circulation is completely independent of the retinal circulation. It is supplied by the long and short posterior and recurrent anterior ciliary arteries and is

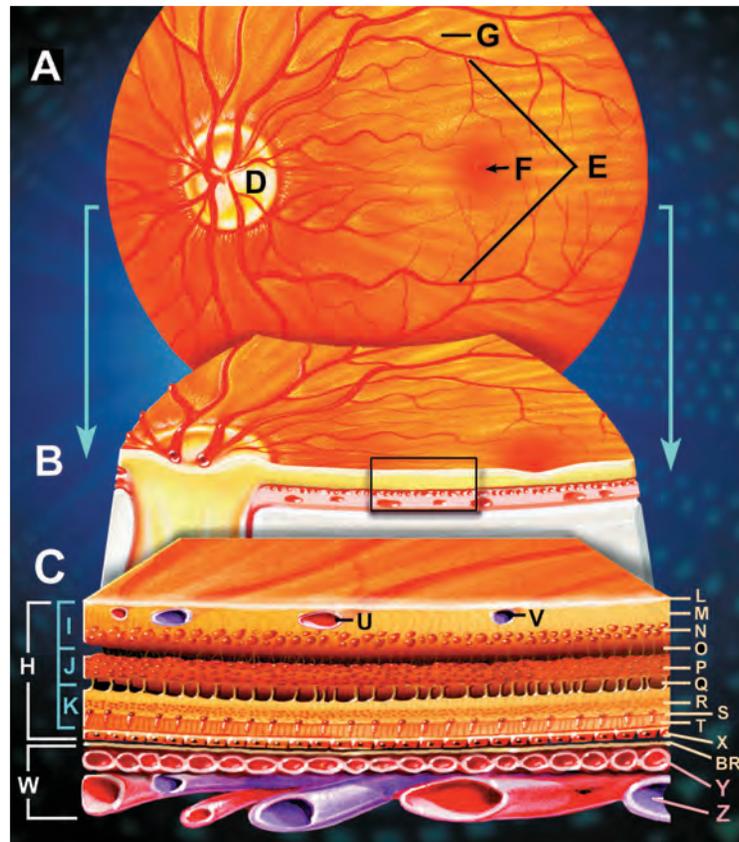


Figure 1: Anatomy of the Normal Retina and Choroid. Anatomy of the normal retina and choroid is displayed. (A) The posterior fundus view shows optic nerve (D), retinal arteries and veins of the parafoveal arcade (E), fovea (F), and visible choroidal vasculature (G) beneath the normal retina. From the oblique cross section (B), an area of the retina and choroid is magnified in (C) to show the direct relationship between clinical ophthalmoscopic fundus view above and its corresponding cellular pathology. Overall layers of the retina (H) include ganglion cell layer (I), layer of intermediary neurons (J), and photoreceptor layer (K). Detailed elements of the retina include inner limiting membrane (L), nerve fiber layer (M), ganglion cells (N), inner plexiform layer (O), inner nuclear layer (P), outer plexiform layer (Q), receptor nuclear layer (R), outer limiting membrane (S), and rods and cones (T)(photoreceptor cells). Retinal arteries (U) and retinal veins (V) run through the nerve fiber layer (M) beneath the inner limiting membrane (L), supplying all cells of the neural retina, except the photoreceptor cells. The photoreceptor cells are supplied by active transport from the choroid (W) through the retinal pigment epithelium (X). The choroid consists of the choriocapillaris (Y) supplied by the larger choroidal vessels (Z). Bruch's membrane (BR) lies between the pigment epithelial cell layer (X) and the choriocapillaris (Y). (Art from Jaypee-Highlights Medical Publishers).



drained by the four mid-peripheral vortex veins (Figure 1C-W). The choroidal capillary system, the choriocapillaris, is located innermost (Figure 1C-Y), its basement membrane forming the outer layer of Bruch's membrane. It has a lobular pattern, with central arterioles feeding capillary beds drained by peripheral venules.

The walls of the choroidal capillaries are extremely thin, with multiple fenestrations permitting passive fluid transport from the capillary lumen to the surrounding extravascular space. During fluorescein angiography studies, the fluorescein molecule is sufficiently small to pass readily and rapidly out of the choriocapillaris, but it does not pass through the overlying retinal pigment epithelium (Figure 1C-X).

Retinal Pigment Epithelium

The retinal pigment epithelium (RPE) (Figure 1C-X), is a single layer of pigmented cuboidal cells which are attached to the photoreceptors (Figure 1C-K-T) and whose basal portions lie on Bruch's membrane (Figure 1C-BR). It serves important metabolic functions for the overlying photoreceptors (Figure 1C-K-T) and forms a structural barrier between the sensory retina and choroid that, under normal circumstances, fluorescein dye will not cross.

Because of the presence of pigmented cells, the RPE serves as an optical barrier. Pigment density is not uniform across the whole retina. It is more intense in the macular region, where pigment epithelial cells are tall, columnar, and densely packed, and least in regions anterior to the equator, where these cells are flatter and have a sparsity of pigment granules.

Retina

The most important characteristics of the retina are its functional architecture and its light transmission and absorption properties. The retina is a thin transparent tissue perfused by vessels from the central retinal artery and, in about 30% of eyes, by an additional cilioretinal artery. The cilioretinal artery, when present, fills at the same time as the choroid. Unlike the choroid, the retinal capillaries are not fenestrated, and there is virtually no extracellular space between the densely packed retinal cells. As a result, the retinal vasculature constitutes a "closed system" that stands out in stark optical contrast to the surrounding tissue, especially in fluorescein angiography.

The outer nuclear and plexiform retinal layers of the retina (Figure 1C-Q) have a high concentration of yellow xanthophyll pigment, particularly in the macula, which is

about two disc diameters in size surrounding (but not including) the fovea (Figure 2). The fovea centralis, which lies at 3.5 mm lateral to the optic disc, is specialized for fine visual perception. In the fovea, the cells are all cones. The axons of the receptor cells pass directly to the inner side of the outer plexiform layer, where they connect with dendrites of horizontal and bipolar cells, extending from the inner nuclear layer. Selective absorption of blue light by this pigment produces a relatively darker macular background in fluorescein angiography.

The retina receives its blood supply from two sources: the choriocapillaris and the central retinal artery. The choriocapillaris is a layer of capillaries intimately attached to the outer surface of Bruch's membrane. The choriocapillaris supplies the outer third of the retina, including the outer plexiform and outer nuclear layers, the photoreceptors, the pigment epithelium and all of the fovea. The remaining inner two thirds of the retina is supplied by branches of the central retinal artery.

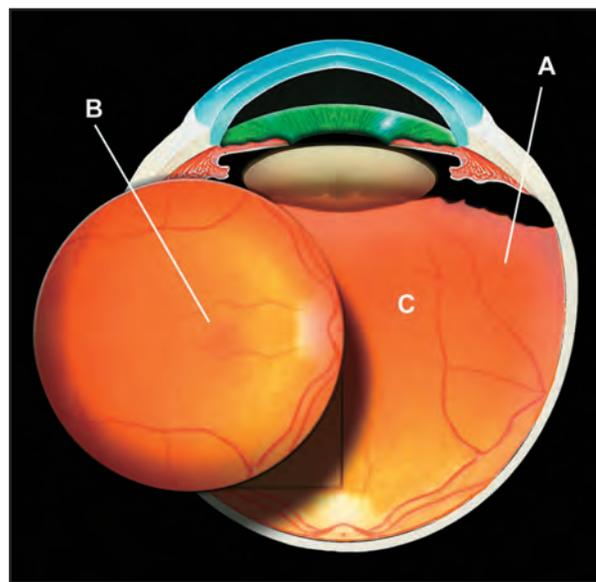


Figure 2: Schematic Representation of the Retina and Related Structures. The retina terminates anteriorly at the ora serrata approximately 7-8 mm posterior to the corneoscleral limbus (A). The macula is clinically an area of altered light reflex which lies 3.5 mm lateral and 1 mm inferior to the edge of the optic nerve (B). The vitreous is a gel of approximately 4.3 ml and is attached anteriorly to the posterior lens capsule, posteriorly to the peripapillary zone and extends centrally to the attachment with the pars plana and anterior retina (C). (Art from Jaypee-Highlights Medical Publishers).

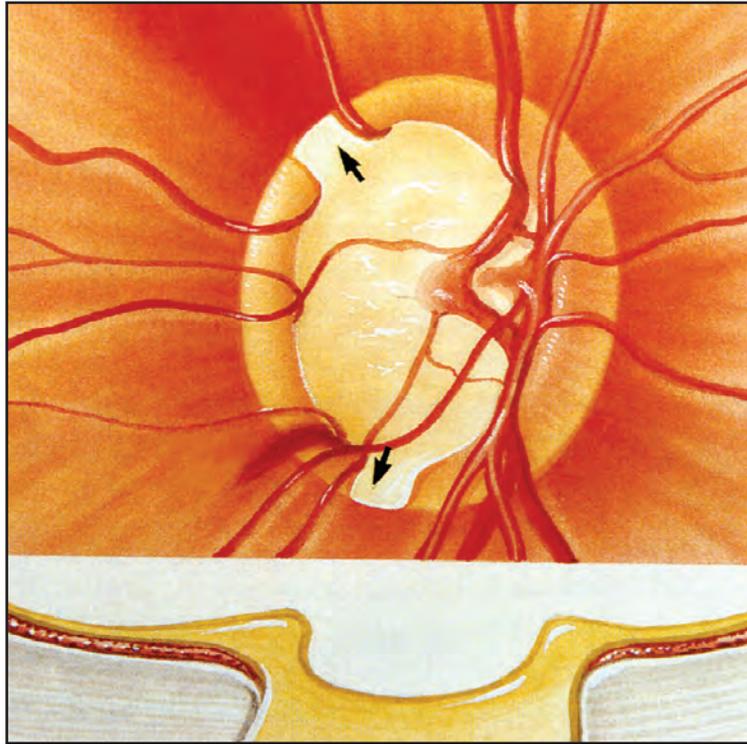


Figure 3: Optic Nerve. All of the approximately one million nerve fibers that receive light signals from the outside world pass through the optic nerve to reach the brain. In glaucoma the number of living, functioning nerve fibers decreases in all directions (arrows) at a rate much faster than would occur through the normal aging process. Their death may be due to increased intraocular pressure (IOP), lack of blood flow, some other mechanism not yet discovered, or a combination of mechanisms. (Art from Jaypee-Highlights Medical Publishers).

Optic Nerve

The optic nerve consists mainly of fibers derived from the ganglionic cells of the retina (Figure 3). These axons terminate in arborizations around the cells in the lateral geniculate body, pulvinar, and superior colliculus which constitute the lower or primary visual centers. From the cells of the lateral geniculate body and the pulvinar fibers pass to the cortical visual center, situated in the cuneus and in

the neighborhood of the calcarine fissure. A few fibers of the optic nerve, of small caliber, pass from the primary centers to the retina and are supposed to govern chemical changes in the retina and also the movements of some of its elements (pigment cells and cones). There are also a few fine fibers, afferent fibers, extending from the retina to the brain, that are supposed to be concerned in pupillary reflexes.

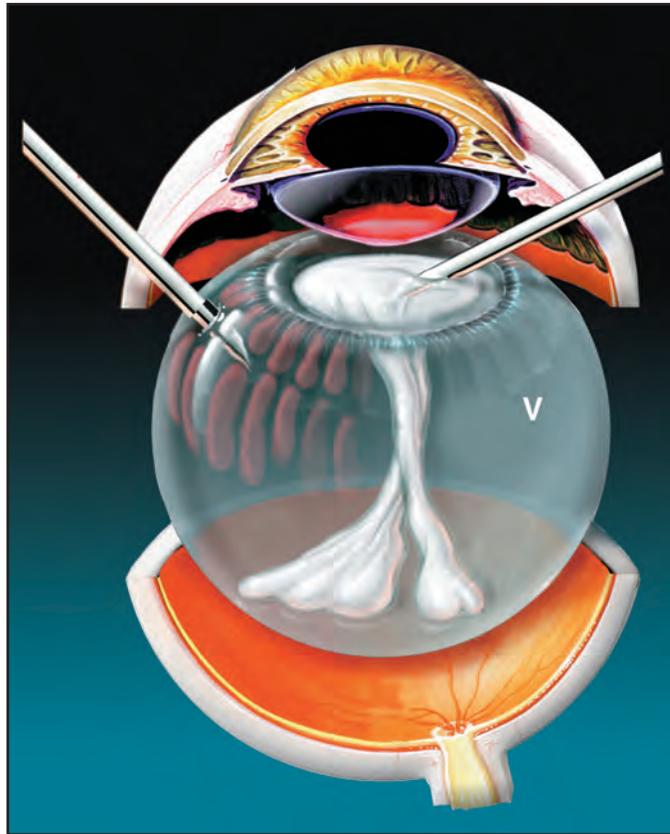


Figure 4: Vitreous (V). The vitreous gel is made up primarily of water (99%) and has only 1% solid, chemical and protein constituents. There are normally no blood vessels within the vitreous gel. Abnormal blood vessels can grow into the vitreous gel in a variety of eye diseases, most commonly diabetic retinopathy. (Art from Jaypee-Highlights Medical Publishers).

The Vitreous

The vitreous is a clear, avascular gelatinous body that fills the space bounded by the lens, retina and the optic disk. Its volume is approximately 80% of the entire globe (Figure 4). The vitreous is the largest single tissue of the human eye with an average volume of 5 ml. Though many people view the vitreous as a relatively inert and optically empty substance, it causes many ocular problems and is secondarily affected by

several retinal and choroidal disorders. The most common pathological vitreous condition is the posterior vitreous detachment.

The basic structure of the vitreous is 1% collagen and hyaluronic acid molecules supported and compartmentalized by a gossamer sacular system of connective tissue; the rest is water. The outer surface—the hyaloid membrane is normally in contact with the posterior lens capsule, the zonular fibers, the pars plana epithelium, the retina and the optic nerve head. The base of the vitreous is



defined as the part in contact with the pars plana epithelium and the retina immediately behind the ora serrata.

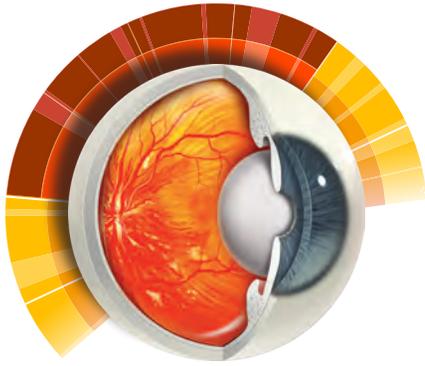
Normal Appearance of the Retina

Because the sensory retina is optically clear, ocular fundus appearance depends on retinal vasculature, degree of melanosis of the retinal epithelium and choroid, and presence or absence of a tapetum. Retinal epithelial cells overlying a tapetum usually are amelanotic so that this region of the ocular fundus appears as the color of the tapetum. In nontapetal regions or eyes having no tapeta, heavily melanotic retinal epithelial cells and choroid impart a dark brown hue to the ocular fundus. Less melanosis leads to lighter shades of brown. As the ocular fundus becomes lighter in color, the deeper structures, such as choroidal vessels or sclera, become

more visible. In some individuals there may be very little retinal epithelial melanin and moderate choroidal melanin so that choroidal vessels, which are somewhat orange and red compared with the red of retinal vessels, are visible in a background of brown. In amelanotic or mildly melanotic eyes, the choroidal vessels will be clearly visible with a white background which is, of course, the sclera.

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2

Fluorescein Angiography

SAMUEL BOYD, MD

Fluorescein angiography has been extensively used for many years. Fluorescein patterns of nearly all the major retinal diseases have been described in numerous books and atlases published by well known retinal specialists. The presentation of this chapter is to provide a practical understanding of the vasculature of the retina, how it functions, identify the main fluorescein angiography patterns, both normal and abnormal, and when is laser treatment indicated.

McLean and Maumenee were the first to use fluorescein dye in living human subjects (1955). In January 1960 Novotny and Alvis performed the first human fluorescein angiogram, and they were the ones who developed the basic photographic system required for sequential documentation of flow through the fundus.

Fluorescein angiography enables us to supplement the information derived from direct clinical visualization with evidence of altered fluid dynamics in the iris, retina, and choroid and to diagnose structural changes in the retina and retinal pigment epithelium.

Several anatomic and physiologic features of the eye must be considered in the

interpretation of fluorescein angiograms. Blood vessels appear larger with angiography than with ophthalmoscopy or color photography. On angiography, the entire caliber of the vessel lumen can be seen, whereas with the other two methods, only the central blood column is visible, and not the marginal layer of clear plasma. Surrounding each retinal artery and, to a lesser extent, each retinal vein, is a small avascular zone. On a high-quality angiogram, the avascular zone around retinal arteries can be seen easily. Only in a few instances, however, can the avascular zone be seen around the veins.

The foveal capillary-free zone may be crossed by a large retinal vessel, but this is rare, and should be regarded as a variant of the normal pattern.

The visibility of the choroid is dependent upon the density and distribution of pigment in the retinal pigment epithelial cells and, to a lesser extent, upon the density of the choroidal pigment. Since the cells of the retinal pigment epithelium are taller and more heavily pigmented in the region of the macula, there is less fluorescence transmitted from the underlying choriocapillaris in this area.



Fluorescein leaks from the choriocapillaris permeates the choroid, and is partially absorbed by the sclera. Areas in which the pigment epithelium is deficient may show fluorescence from the sclera. If a scar is present in any area, it may be stained by fluorescein, causing it to fluoresce.

In a normal eye, the optic nerve head is fluorescent after the passage of dye from the circulatory system. Dye from the choriocapillaris at the margin of the nerve head permeates the nerve head. Because there is some degree of normal fluorescein leakage from the ciliary body, the anterior chamber and vitreous also will contain some dye.

According to experts, five factors are inter-related to obtain the most value from fluorescein angiography: the physical and chemical properties of fluorescein dye, the anatomy of the human eye, the proficiency of the photographers, the sophistication of the recording equipment, and (most critically) the skill of the professional at correctly interpreting the information and relating it to other clinical findings.

The Fluorescein Dye

Clinical and Physical Properties

Sodium fluorescein is a stable, highly water-soluble, pharmacologically inert, inexpensive and relatively safe substance. It fluoresces at normal blood pH, and absorbs and emits light within the visible range of the spectrum, permitting the use of standard photographic equipment and supplies.

Physiologically the sodium fluorescein molecule is small enough to diffuse rapidly within fluid compartments yet sufficiently large not to pass through the tight endothelial junctions of intact retinal blood vessels and the retinal pigment epithelium. When stimulated

by light, this dye re-emits light of a longer wavelength and lower energy level almost instantaneously.

How to Use It

The solution is injected intravenously. There are several alternatives for its administration:

- 1) Use a solution of 10% sodium fluorescein (5 ml).
- 2) Use a 25% solution in smaller quantities. Some investigators have obtained equally satisfactory results, with fewer adverse effects with this second alternative, or even smaller injections (2 ml) of the standard 10% solution (Table 1).

Table 1. Normal Circulatory Filling

0	sec	— injection of fluorescein
9.5	sec	— posterior ciliary arteries
10	sec	— choroidal flush (or “pre-arterial phase”)
10-12	sec	— retinal arterial stage
13	sec	— capillary transition stage
14-15	sec	— early venous stage (or “lamellar stage”, “arterial-venous stage”)
16-17	sec	— venous stage
18-20	sec	— late venous stage
5	mins	— late staining

Fluorescein enters the ocular circulation from the internal carotid artery via the ophthalmic artery. The ophthalmic artery supplies the choroid via the short posterior ciliary arteries and the retina via the central retinal artery, however, the route to the choroid is typically less circuitous than the route to the retina. This accounts for the short delay between the “choroidal flush” and retinal filling.



Side Effects

Transient nausea and occasional vomiting 30 to 60 seconds after administration are the most common reactions, experienced in fewer than 5% of patients. Moderate adverse reactions, occurring in fewer than 1% of patients, include thrombophlebitis, nerve palsy, temperature elevation, and localized tissue necrosis. There is a very low incidence of severe potentially life-threatening reactions such as laryngeal edema, bronchospasm, anaphylaxis, circulatory shock, and myocardial infarction. Yannuzzi et al have reported a single death among 220,000 fluorescein angiography studies surveyed.

The Different Phases of Fluorescein Studies

Fluorescein angiography documents both the static functional anatomy and the fluid dynamics of the eye. When the interpretation is being made, it is important to review the proper sequence of phases.

Fluorescein studies are typically divided into four phases: pre-filling, transit, recirculation, and late.

1) The pre-filling or pre-arterial phase occurs after administration but before fluorescein dye enters the circulation of the eye. Angiograms taken during the pre-filling phase are useful controls to establish background levels of pseudofluorescence or autofluorescence that might otherwise lead to interpretation errors.

2) The transit phase corresponds to the first complete passage of fluorescein through the choroidal and retinal vasculature, and occurs within about 30 seconds of dye injection. Following perfusion of the choroid and choriocapillaris, there are three functional subdivisions of the transit phase: the arterial phase, which corresponds to complete arterial filling, the capillary (and arteriovenous) phase, which

culminates in the first evidence of laminar venous flow, and the venous filling (or laminar) phase, which occurs as the veins completely fill and the arteries begin to empty of dye.

3) The recirculation phase corresponds to the first return of fluorescein bearing blood to the eye after its passage through the general circulation, and is complete about 3 minutes into the study. Recirculation fluorescence is considerably dimmer than transit fluorescence. Early staining or leakage is generally noted during this stage of the study.

4) The late (or elimination) phase represents the complete removal of fluorescein dye from the circulation, leaving only spots of residual leakage and late staining. For all practical purposes, elimination is virtually complete 30 minutes after administration.

Normal Angiographic Pattern

Sequence of Events

The interpretation of any angiogram, whether normal or abnormal, requires the evaluation of each anatomic component of the posterior portion of the eye; the choroid, retina, disc, and macula. Each component must be evaluated at specified time intervals. It is helpful to analyze an angiogram with respect to the pathologic lesions that may be seen at different stages and in different locations.

The illustrations shown in Figures 1A, 2A, 3, 4, 5A, 6A, 7A, and 10A, are special creations by Jaypee-Highlights to show the function of the retinal vasculature through fluorescein studies during different stages of the circulation. The figures on the right side of each of these illustrations are actual fluorescein angiography photos that reveal the appearance of each of those stages during angiography.



After fluorescein is injected into the antecubital vein, the time it takes to reach the eye depends upon the patient's arm-to-retina circulation time. This is typically 12 to 15 seconds. However it can range from 5 to 30 seconds, depending upon cardiac output, viscosity of the blood, and the caliber of the blood vessels. Circulation time will increase with the presence of any disease that affects the myocardium and great vessels, causing congestion in the pulmonary and systemic circulation or obstruction in the vascular system.

During the pre-arterial or pre-filling phase, fluorescein enters the choroidal vasculature through the posterior ciliary arteries. In a very lightly pigmented fundus, filling of large choroidal arterioles may be faintly perceived (Figures 1A and 1B) although in general the first discernible presence of fluorescein is the patchy background corresponding to perfusion or early filling of the choriocapillaris (Figures 2A and 2B).

Even in normal patients, the filling pattern of the choriocapillaris is patchy and variable. In most studies, details of the choriocapillaris are not discernible, and only a "choroidal flush"

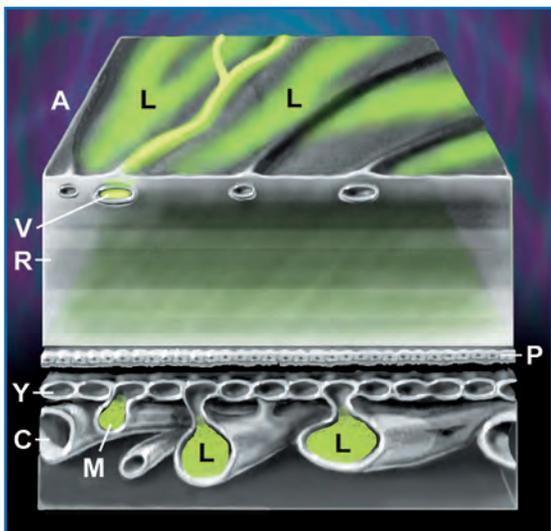


Figure 1-A: Early Filling of Large and Medium Sized Choroidal Arterioles. This series of illustrations shows the retina (R) and choroid (C) in cross section during fluorescein angiography, along with its corresponding magnified fundus appearance at each stage above at (A). First, there is early filling of large (L) and medium sized (M) choroidal arterioles with fluorescein (green) as seen in the fundus and cross section views. The fluorescein has not reached the level of the choriocapillaris (Y) at this stage. Note early filling of a retinal vessel (V) located within the nerve fiber layer (N) of the retina. (Art from Jaypee-Highlights Medical Publishers Inc.).



Figure 1-B: Early Filling of Large and Medium Sized Choroidal Arterioles with Fluorescein. Earliest phase of the fluorescein study. (Photograph presented as a courtesy of William Tasman from his classic book "Clinical Decisions in Medical Retinal Disease", Chapter 1 by Jay Federman, M.D., published by Mosby, Inc., 1994.)

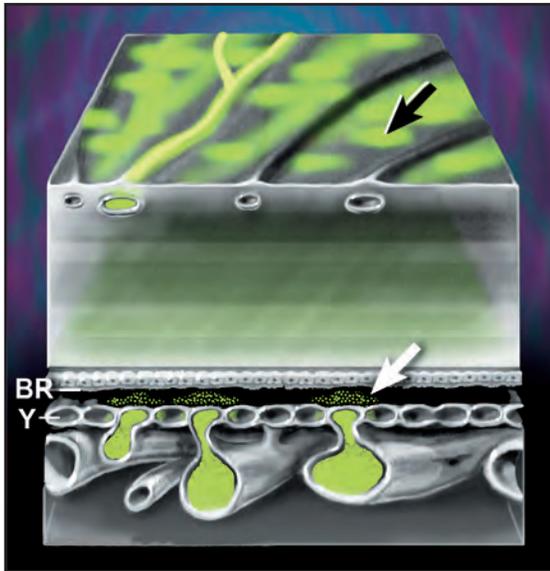


Figure 2-A: Early Filling of the Choriocapillaris. Shown is early filling of the choriocapillaris (Y) with fluorescein (green). As seen in the fundus view, the fluorescein flows in a patchy manner (black arrow) from the efferent side of the circulation. Some is beginning to leak into the extravascular space (white arrow) near Bruch's membrane (BR). (Art from Jaypee-Highlights Medical Publishers Inc.).

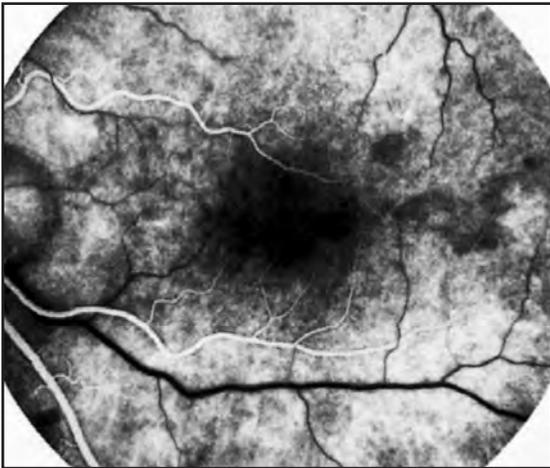


Figure 2-B: Early Filling of the Choriocapillaris with Fluorescein. Medium-sized and smaller arterioles are seen leading to patches of fluorescein filled choriocapillaris. (Photograph presented as a courtesy of William Tasman from his classic book "Clinical Decisions in Medical Retinal Disease", Chapter 1 by Jay Federman, M.D., published by Mosby, Inc., 1994.)'

will appear on the angiogram. Shortly after filling of the choriocapillaris, the first appearance of fluorescein in the arteries signifies the beginning in transit of the arterial phase, which extends until the arteries are completely filled.

Because of the capillary fenestrations in the choriocapillaris, intravascular choroidal fluorescein rapidly leaks into the extravascular space (Figure 2A), beginning at the inner choroidal layers directly below Bruch's membrane (Figure 3).

Fluorescein diffuses throughout the inner choroidal layers, rapidly reaching equilibrium between the intravascular and extravascular compartments and including the inner scleral

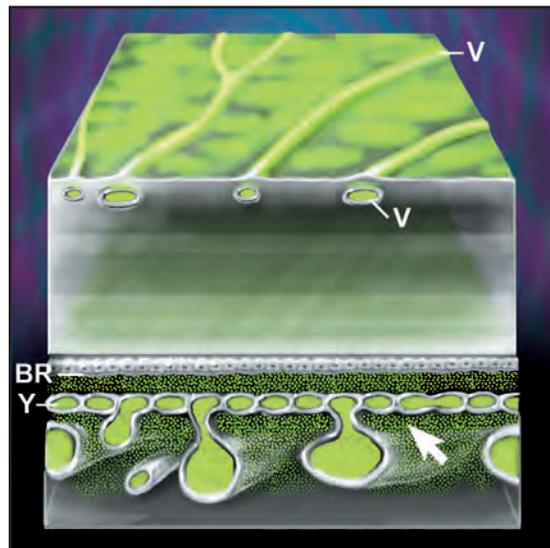


Figure 3: Complete Filling of the Choriocapillaris. Next follows complete filling of the choriocapillaris (Y) with fluorescein (green). The fluorescein has now begun to leak into the extravascular choroidal stroma. An extravascular flush appears in Bruch's membrane (BR) and the extravascular inner choroidal layers (arrow). There is filling of additional retinal vessels (V) located within the nerve fiber layer of the retina. Note the appearance of the complete filling of the choriocapillaris in the fundus view above. (Art from Jaypee-Highlights Medical Publishers Inc.).



fibers (Figure 4). During the somewhat later venous filling phase of the study extravascular fluorescein begins to appear, to a lesser extent, in the stroma of the outer choroid (Figure 4).

As the study progresses, the process of choroidal perfusion is reversed. The combined result of dye leakage, elimination, and distribution through the entire blood volume is that the intravascular fluorescein concentration quickly drops below the extravascular concentration.

Beginning in the inner choroidal layers, the medium-sized choroidal vessels are darkly silhouetted against the still fluorescent extravascular background (Figure 5A-B).

The recirculation phase of the angiogram follows the transit phase and represents the first return of blood containing fluorescein (a small amount) to the eye. This occurs after the blood has passed through the kidneys.

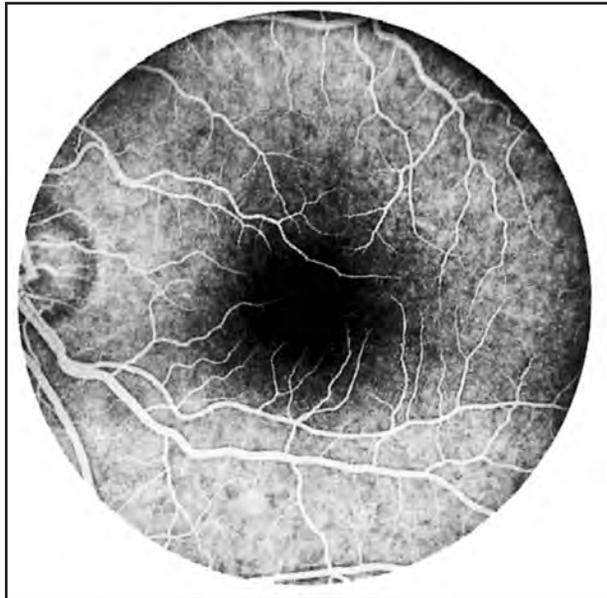


Figure 4: Complete Filling of Intravascular and Extravascular Components of the Inner Choroid. The intravascular and extravascular components of the inner choroid are now evenly filled with dye, completely obscuring all choroidal detail. (Photograph presented as a courtesy of William Tasman from his classic book "Clinical Decisions in Medical Retinal Disease", Chapter 1 by Jay Federman, M.D., published by Mosby, Inc., 1994.)

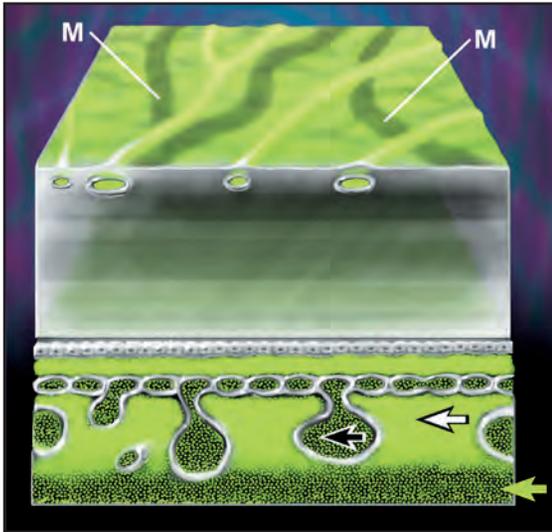


Figure 5A: Visualization of Medium-sized Choroidal Vessels. As fluorescein re-circulates and is diluted through the entire blood volume, the intravascular choroidal concentration (black arrow) drops below the extravascular concentration (white arrow). The concentration in the outer choroidal extravascular space (green arrow) is the same as within the entire choroidal intravascular space (black arrow). Since the concentration is greater in the inner choroidal layers, medium-sized vessels (M) within the inner and middle choroid, as seen in the fundus view, can be visualized during the early phases of the study. Note that these medium-sized choroidal vessels stand out in dark relief against the more concentrated dye in the extravascular inner choroidal space. (Art from Jaypee-Highlights Medical Publishers Inc.).



Figure 5B: (Photograph presented as a courtesy of William Tasman from his classic book "Clinical Decisions in Medical Retinal Disease", Chapter 1 by Jay Federman, M.D., published by Mosby, Inc. 1994).



As observed over time, fluorescein leaks back into the choroidal vessels from, successively, the choriocapillaris, outer choroid, and inner scleral layers. During the later stages of this process the extravascular fluorescein concentration is greater in the outer choroid than in the inner choroid, and large choroidal vessels stand out in dark relief (Figures 6A-B) The fluorescence in the recirculation phase is very dim in contrast to that of the transit phase in which the dye in the blood is in much higher concentration.

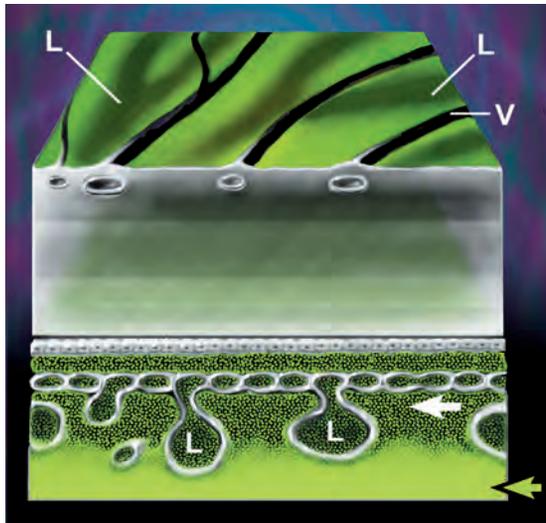
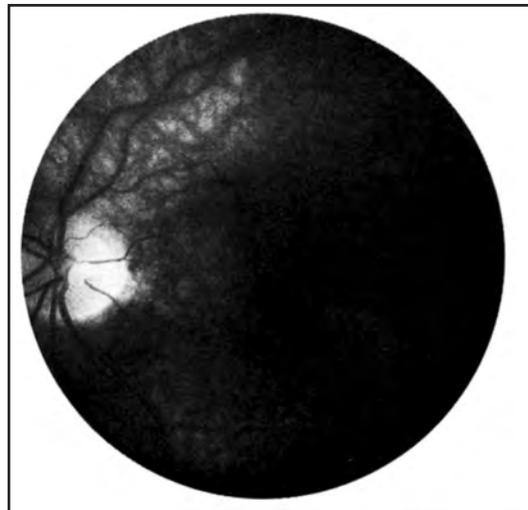


Figure 6-A: Visualization of Large Choroidal Vessels. As the recirculation phase progresses, fluorescein concentrations in the inner and outer choroid become equal (not shown). In the later and elimination phases, the extravascular concentration in the inner choroid (white arrow) continues to drop below that in the more slowly purged outer choroid layers (green arrow). Large vessels (L) in the outer choroid layers are surrounded by extravascular regions with much higher fluorescein concentration (green arrow). These large vessels (L) can be visualized in dark relief as seen in the fundus view above. Note that the retinal vessels (V) within the nerve fiber layer of the retina have now been purged of dye, and also appear in dark relief against the light background of the remaining dye within the outer choroid. (Art from *Jaypee-Highlights Medical Publishers Inc.*).

The zonula occludens of the retinal pigment epithelium prevents diffusion or transport of fluorescein directly from the choroid to the outer retinal layers. Approximately 1 second after the choroidal flush, fluorescence is perceived in the central column of large arterioles, and rapidly increases in intensity, filling the arterioles completely.

Fluorescein next crosses the capillary network, revealing fine details of its structure in the perifoveal region where background choroidal fluorescence is masked by the densely pigmented RPE.

Figure 6B: Visualization of large choroidal vessels. Large vessels in the outer choroid layers stand out in dark relief against the more concentrated extravascular fluorescein. (Photograph presented as a courtesy of William Tasman from his classic book "Clinical Decisions in Medical Retinal Disease", Chapter 1 by Jay Federman, M.D., published by Mosby, Inc., 1994.)



Abnormal vessels that may be supplied by the choroidal system, such as neovascularization of the disc in diabetic retinopathy and subretinal neovascularization in senile macular degeneration and ocular histoplasmosis syndrome, often fill before the normal retinal vessels.

ABNORMAL ANGIOGRAPHIC PATTERNS

Hyperfluorescence and Hypofluorescence

Abnormal fluorescein angiographic patterns result from disruption of the normal functional relationships between the various structures in the eye. The terms “hyperfluorescence” and “hypofluorescence” are the key abnormalities. They refer to departures from the normal pattern of fluorescence in the eye. They may relate to various ocular pathologies.

Hyperfluorescence may correspond to:

- 1) the presence of fluorescein in a location where it is not normally found as shown in Figs. 7AB, 8, 9.
- 2) an abnormally high concentration of fluorescein in an appropriate location, and/or
- 3) abnormal visibility of a normal dye distribution and concentration because of defects in overlying structures that would ordinarily obscure it such as the RPE.

Hypofluorescence may be caused by:

- 1) the complete absence of fluorescein in a location where it is normally found,
- 2) an abnormally low concentration of fluorescein in some region, and/or
- 3) the abnormally obstructed visibility of light from normal dye distribution and concentration because of overlying pathology.

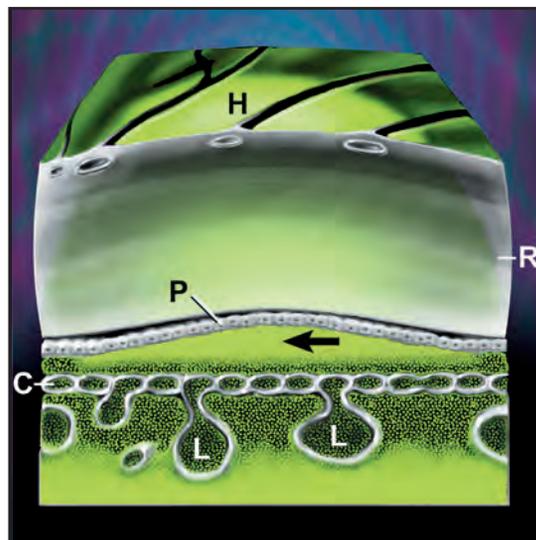


Figure 7A: Hyperfluorescence of a Retinal Pigment Epithelium Detachment. An example of hyperfluorescence (H) seen in the fundus view is due to accumulation of dye in an abnormal location (arrow), in this particular case, a localized serous detachment of the retinal pigment epithelium (P). Retina (R), choriocapillaris (Y) and large choroidal vessels (L). (Art from Jaypee-Highlights Medical Publishers Inc.).

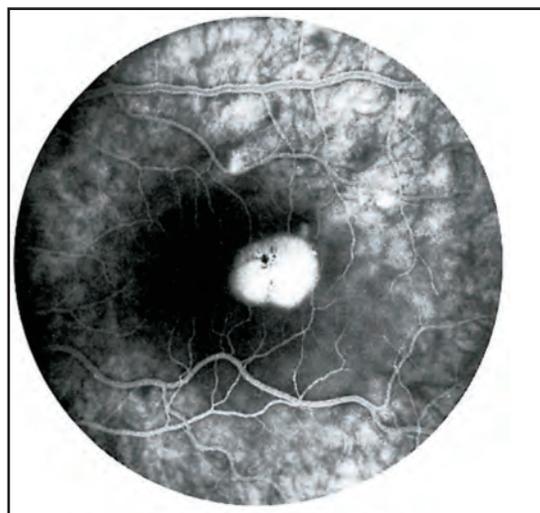


Figure 7B: Hyperfluorescence in a patient with retinal pigment epithelium detachment. This localized area or hyperfluorescence has resulted from an accumulation or dye under the RPE. (Photograph presented as a courtesy of William Tasman from his classic book “Clinical Decisions in Medical Retinal Disease”, Chapter 1 by Jay Federman, M.D., published by Mosby, Inc., 1994).



Hyperfluorescence

An excellent example of hyperfluorescence caused by the accumulation of dye in an abnormal location is found in focal detachment of the retinal pigment epithelium (Figures 7A-B). Dye-containing fluid that accumulates between the RPE and Bruch's membrane in the region of the serous detachment of the RPE produces a hyperfluorescent patch with sharp and abrupt borders (Figure 7B).

Fluorescein angiography, is useful to exclude disorders such as hemorrhage under the

retinal pigment epithelium or retina. Fluorescein angiography may provide useful information in the evaluation of malignant melanomas which include early mottled or patchy hyperfluorescence (Figure 8) and discrete pinpoint leakage (Figure 9).

Solid tumors such as choroidal melanomas or metastatic lesions show hyperfluorescence caused by elevated fluorescein dye concentrations in the uveal stroma near the tumor site (Figures 8 and 9). The increased vascularity of these tumors results in early-phase hyperfluorescence of vessels. Fluorescein then leaks into the extravascular space. Choroidal hemangiomas



Figure 8: Patchy Hyperfluorescence from Malignant Melanoma. A 67 year old female was found to have a pigmented tumor in her left eye. Her visual acuity was reduced to 20/60 due to a macular pucker. The tumor measured 11 mm in diameter and was 2.4 mm thick. On fluorescein angiography, the tumor showed a mottled and patchy hyperfluorescence. (Photo courtesy of Robert Johnson, M.D.)

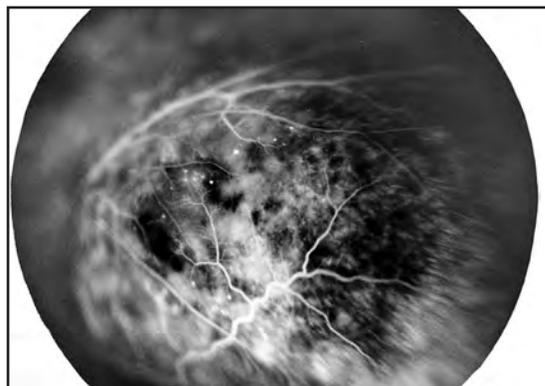


Figure 9: Hyperfluorescence with Pinpoint Leakage in Malignant Melanoma. A 79 year old female noted blurred vision in her left eye. The visual acuity measured 20/50 due to diabetic retinopathy. A 12 mm diameter pigmented choroidal mass was found. The maximal thickness measured 5.9 mm. Note the hyperfluorescence over the tumor with several punctate areas of hyperfluorescence. (Photo courtesy of Robert Johnson, M.D.)

also demonstrate hyperfluorescence at very early phases of angiographic studies.

Other conditions which show hyperfluorescence are central serous chorioretinopathy, in which the dye accumulates between the neurosensory retina and the RPE to produce a diffuse region of hyperfluorescence.

In ocular histoplasmosis, nodular elevation of the RPE by choroidal neovascular membranes may cause choroidal hyperfluorescence.

Hypofluorescence

The absence of fluorescein in a location where it is normally found may be attributable to either a lack of perfusion or the absence of tissue itself. In patients with a coloboma there is early-phase hypofluorescence because the choriocapillaris is missing. Only the large vessels of the choroidal vasculature fluoresce and are clearly visible without the obstruction of an overlying RPE.

Hypofluorescence is also caused by blocked transmission of choroidal fluorescence. This may occur when fluid, exudates, hemorrhage, pigment, scar, inflammatory material, etc. accumulates in front of the choroidal vasculature and deep to the retinal vasculature.

A hemorrhagic detachment of the RPE produces a corresponding region of hypofluorescence (Figures 10A-B). A choroidal nevus is hypofluorescent, presumably because the crowded pigmented cells of the nevus displace and block fluorescein dye.

Another cause of abnormal hypofluorescence is attributable to vascular filling defects. With blocked fluorescence, the fluorescein is present in the circulations of the fundus, but is not visible because a tissue or fluid barrier

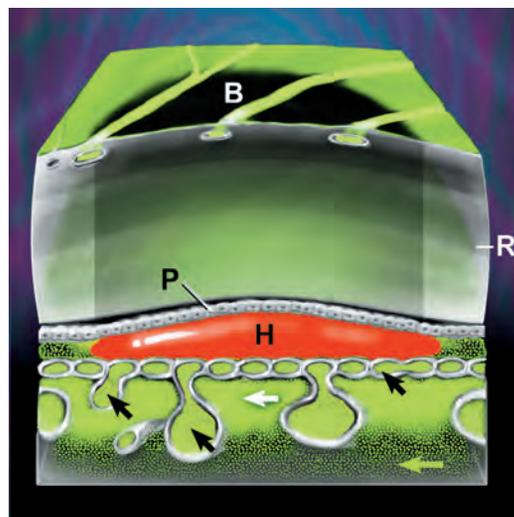


Figure 10A: Hypofluorescence of a Hemorrhagic Detachment of the RPE. Shown is hypofluorescence in a patient with hemorrhage (H) under the retinal pigment epithelium (P). There is normal fluorescein perfusion of the intravascular (black arrows) and extravascular (white and green arrow) choroidal spaces, but transmission is blocked (B), as seen in the fundus view, by an overlying hemorrhagic RPE detachment (P,H). Retina (R). (Art from Jaypee-Highlights Medical Publishers Inc.).



Figure 10B: Hypofluorescence in a Patient with Hemorrhage Under the Retinal Pigment Epithelium. The corresponding hypofluorescent area is due to blockage or obscuration of the normal choroidal fluorescence by hemorrhagic detachment of the RPE. (Photograph presented as a courtesy of William Tasman from his classic book "Clinical Decisions in Medical Retinal Disease", Chapter 1 by Jay Federman, M.D., published by Mosby, Inc., 1994).



conceals it. With a vascular filling defect, fluorescein can not be seen because it is not present. Since fluorescein reaches the retina and choroid by way of vessels, lack of the fluorescein dye in either vascular system indicates an obstructive problem.

Choroidal Vascular Filling Defect

The normal choroidal vasculature is usually difficult to document with fluorescein angiography because of the pigment epithelial barrier. When choroidal vascular filling defects exist, the pigment epithelium is often secondarily depigmented or atrophied. In these cases the hypofluorescence caused by the vascular filling abnormality of the choroid and choriocapillaris can be documented angiographically.

When choroidal vessels do not fill, dark patches of hypofluorescence beneath the retina appear early in the angiogram. The distribution and morphology of the hypofluorescence vary according to the disease process. Because the choroidal circulation is completely separate from the retinal circulation, choroidal vascular filling defects do not correlate with the retinal vascular distribution.

ANGIOGRAPHIC INTERPRETATION OF MOST IMPORTANT PATHOLOGICAL CONDITIONS

Diabetic Retinopathy

Non-Proliferative Diabetic Retinopathy

In non-proliferative (background) retinopathy, the very earliest sign that can

be detected by fluorescein angiography is the dilatation of the retinal veins. It also can be seen that the walls of the veins are damaged in the areas showing staining with fluorescein dye. Subsequent changes are the appearance of microaneurysms, hemorrhages and exudates. As the number of microaneurysms increases, many of the retinal capillaries lose their pericytes and endothelial cells, and become nonfunctional. These areas of nonfunctional capillaries are demonstrated angiographically to be non-perfused. If an area of non-perfusion becomes quite large, it may appear as cotton-wool spots.

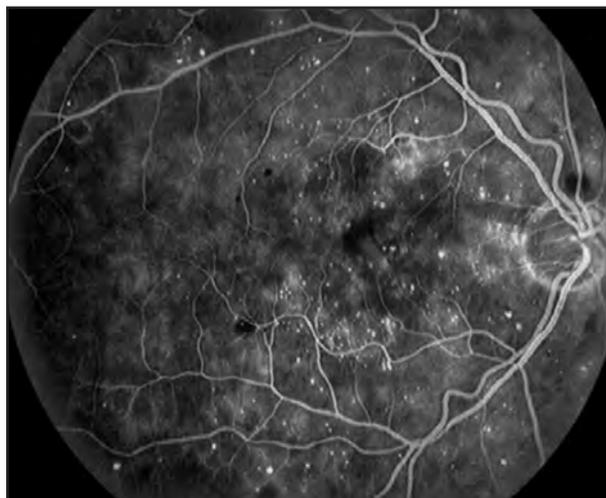
Pre-Proliferative Diabetic Retinopathy

Between non-proliferative and proliferative retinopathy, there is a pattern of retinal changes that has been called pre-proliferative diabetic retinopathy. These changes such as soft exudates (cotton-wool spots), venous abnormalities and intraretinal microvascular abnormalities (IRMA), can be well demonstrated by angiography as a flat network of tortuous capillaries that do not follow the normal capillary network and do leak (Figure 11)

Proliferative Diabetic Retinopathy

The appearance of new vessel formation either on the disc or elsewhere in the retina signals a proliferative diabetic retinopathy. It can be shown by angiography in many eyes in whom neovascularization is present on the disc. The new vessel formation on the disc fills with fluorescein before most of the retinal vessels. New vessels elsewhere in the retina appear to fill with the arterial phase of the angiogram. In the late stages of the

Figure 11: Non-Proliferative Diabetic Retinopathy. Observe in this stage of the disease how focal areas of hyperfluorescence and capillary non-perfusion are present, with areas of leakage around the microaneurysms. (Courtesy of Samuel Boyd., M.D.)



angiogram, there is a marked leakage of dye from the fronds of the vessels and subsequent filling of the vitreous with fluorescein.

Retinal Vein Occlusions

In central retinal vein occlusion, the red-free photograph shows a combination of dilated and tortuous veins, intraretinal hemorrhages and blurred disc margins. The marked dilatation and tortuosity of the veins can be appreciated while their walls become stained with the fluorescein dye.

The most characteristic appearance of a branch retinal vein occlusion is its limitation of involvement to one side of the horizontal raphe. The site of the venous occlusion often appears as a hyperfluorescent area on angiography. The fluorescein dye often shows an increase in retinal venous circulation time distal to the site of obstruction (Figure 12).

Angiography is especially useful in documenting the extent of the macular edema in selected macular venous occlusions. Late photos are useful in detecting the presence or absence of cystoid spaces.



Central Serous Chorioretinopathy

Central serous retinopathy, also known as serous detachment of the sensory retina, is a spontaneous detachment of the sensory retina. At the beginning there is a small area of fluorescein leakage into a larger blister-like elevation of the sensory retina. Fluorescein dye diffuses throughout the volume of the serous elevation. The early venous phase shows the area of leakage identified in a small point. The late venous phase shows the extension of the fluid adopting a particular configuration (smokestack) into a large serous detachment under the sensory retina. The margins of the lesion are usually fairly well defined showing the extent of the sensory detachment (Figure 13).

Cystoid Macular Edema

This type of macular edema is a recognized complication of cataract extraction. This condition is characterized by radial separation of the nerve fibers and subsequent collection of pockets of fluid. Fluorescein accumulation may not be noticeable by angiography until quite late, requiring photographs at 30 minutes after dye injection. A characteristic "flower-petal" pattern appears on the angiogram during the late arteriovenous phase.

Age-Related Macular Degeneration: Sub-Retinal Neovascularization

Sub-retinal neovascularization is characterized by the presence of a tuft of vessels under the retinal pigment epithelium. This type of degeneration is associated with drusen, pigmentary and atrophic changes in

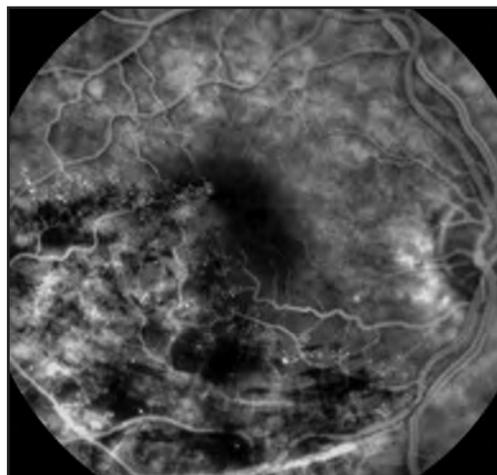


Figure 12: Superior Branch Retinal Vein Occlusion. In this case there is some staining of the wall of the affected branch vein in the occluded area. You may observe also the areas of non-perfusion of the capillary bed and leakage from unobstructed capillaries. Blockage of fluorescence by hemorrhages and persistent macular edema. (Courtesy of Samuel Boyd, M.D.)

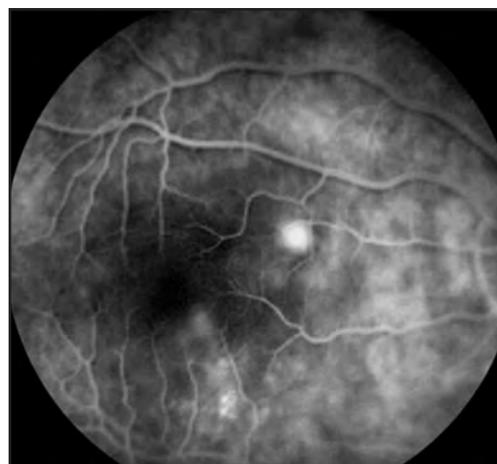


Figure 13: Central Serous Chorioretinopathy. Characteristically, the venous phase of the angiogram shows the area of leakage. The late venous phase will demonstrate extravasation of fluorescein under the sensory retina resembling the typical fluorescent balloon-type image. Such pattern occurs because of a small break in the retinal pigment epithelium and Bruch's membrane. (Courtesy of Samuel Boyd, M.D.)

the retinal pigment epithelium, serous and hemorrhagic detachments of the retinal pigment epithelium and sensory retina.

The new sub-retinal vessels fill with fluorescein at an earlier (pre-arterial) phase of the angiogram than do most other retinal vessels. In the presence of subretinal blood, this may appear like a black zone around the neovascular net (Figure 14).

Retinoblastoma

Retinoblastoma is predominantly a tumor of infancy (between 2-6 years old). The whitish color reflex of the tumor through the pupil is very characteristic, especially in its endophytic phase. The tumor may extend from the optic nerve throughout the orbit and/or the brain. Its main characteristics are the intratumoral calcifications and the presence of seeds floating in the vitreous. In cases of endophytic tumors a second circulation is visible. The fluorescein angiogram shows dye leakage into the tumor and staining of the tumor at different stages. During the early phase of the angiogram there is minimal leakage into the tumor evolving to extensive staining of the lesion at later stages of the angiogram.

Recent Developments in Fluorescein Angiography

Two important improvements have refined the use of fluorescein angiography. First, the ability to digitize images and to use the overlay techniques have helped to assess



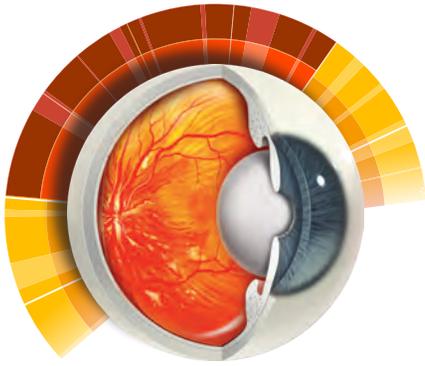
Figure 14: Sub-Retinal Neovascularization. SRNV may have angiographically a variety of appearances. Differentiation between the two typical patterns (classic and occult) is important for treatment guidelines. Here you may observe a well-demarcated area of hyperfluorescence with significant leakage in the subretinal space. This picture shows an extrafoveal lesion with a better prognosis for the patient. (Courtesy of Samuel Boyd., M.D.)

how effective laser photocoagulation has been and to minimize the area of destruction of the retina and the choriocapillaris by having better control of imaging.

The second improvement is the capacity for continuous recording of angiography through video techniques. This technology enables us to view and detect specific new aspects of long familiar problems in different retinal disorders.

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3

Introduction to Optical Coherence Tomography

ROSARIO BRANCATO, MD.,
L. PIERRO, MD

Optical Coherence Tomography (OCT) is a modern diagnostic imaging technique that enables the visualization “in vivo” of the cross sectional structure of the retina, the vitreo-retina interface and the anterior segment of the eye with higher resolution than any other non invasive imaging technique.

It is based on a complex analysis of the reflections of low coherence radiation from the tissue under examination.

The resolution available with current instrumentation at present varies approximately from 5 to 10 microns, according to the instruments used. These imaging techniques, which can provide cross-sectional images of intraocular structures, give important diagnostic information complementary to conventional fundus photography, fluorescein angiography and indocyanine green angiography.

OCT is rapidly emerging as a basic imaging tool for the diagnosis and consequently for the control of the evolution of macular diseases: diabetic retinopathy, age-related-macular degen-

eration, macular holes, epiretinal membranes and other retinal diseases.

The discomfort of patients is minimized because the acquisition of the images is rapid and this permits us to acquire many images in different cross-sectional planes of the retina, the vitreo-retina interface and also of the anterior segment of the eye.

OCT images contain much information on the retina structure and have an important role in the evaluation of the disease progression and the response to therapy.

The introduction of OCT systems, using Spectral/Fourier domain, has allowed a higher resolution of the retinal images and a faster images acquisition.

In the past, fluorescein angiography (FA) and indocyanine green angiography (ICGA) have allowed visualization of the retinal vessels; today OCT allows the visualization of the structure of the retina, the retinal pigment epithelium and the choriocapillary inner spaces and highlights



the vitreoretinal interspace. Moreover, OCT can quantify thickness of the retina, the amount of subretinal fluid and the pigment epithelium. For all these aspects OCT is today a very important tool for the assessment of the macular diseases, in the choice of the treatment and in the follow-up of the evolution of chorioretinal diseases.

What is OCT?

OCT uses near infrared, low coherence light to achieve a resolution of approximately 5-10 microns, depending on the instrument used. Similar to an ultrasound which uses sound waves, a CT scan which uses X-rays, and an MRI which uses electron spin resonance, OCT uses light to obtain a cross-sectional image. It uses a non-contact transpupillary approach to obtain a tomograph of the retina which is displayed in real time through a computer. The scan length for each tomogram may be between 2.83 and 12 mm. Quantitative measurement of retinal thickness is possible because of the well-defined boundaries of optical reflectivity at the inner and outer margins of the neurosensory retina. Quantification of juxtapapillary Retinal Nerve Fiber Layer (RNFL) thickness in glaucomatous eyes is also available. Circular scans around the optic nerve, with a circle diameter of either 2.25 or 3.37 mm, without overlapping the disc itself, can be performed. These measurements are obtained by means of a computer algorithm that searches for the characteristic changes. A transverse sequence of optical ranging measurements is used to construct a false color tomographic image of tissue microstructure which appears incredibly similar to a histologic section. Spectral OCT today can function as a type of "Optical Biopsy" in an even more precise way. Since OCT is based

on near-infrared interferometry, it is not affected by axial length, refraction or by the degree of nuclear sclerosis; however large posterior sub-capsular or cortical cataracts, as well as a poor compliance of the patient, do impair the ability to perform OCT. This technology is capable of reproducible measurement of retinal thickness in normal eyes^(1,2,3).

Interpretation of OCT Maps

OCT images can be presented as either cross sectional images or as topographic maps. Cross-sectional or B-mode imaging is accomplished by acquiring a sequence of 100 interferometric A-scans across a section of retina. To facilitate interpretation a false color scheme is added in which bright colors such as red and white correspond to highly reflective areas and darker colors such as blue and black correspond to areas of lower reflectivity. Topographic maps obtained by OCT are displayed by a false-color scheme to facilitate interpretation. For cross-sectional images, bright colors correspond to areas of high reflectivity while darker colors correspond to areas of low reflectivity. For topographic maps, bright colors are assigned to areas with increased retinal thickening and darker colors are assigned to areas with less retinal thickness.

Retinal thickness is converted to a false color value for each of the 600 points measured within 3,000 microns from the center. Interpolation of polar coordinates is performed to estimate thickness in the wedge-shaped areas between each cross-sectional scan. To further facilitate interpretation, the macula is divided into 9 ETDRS regions with a central circle of 500 μm radius. Two outer circles with radii of 1,500 μm and 3,000 μm complete the display.

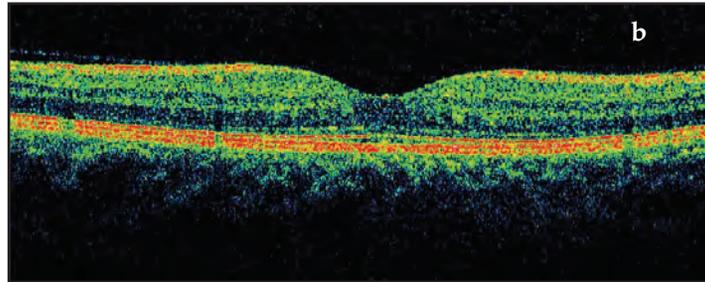
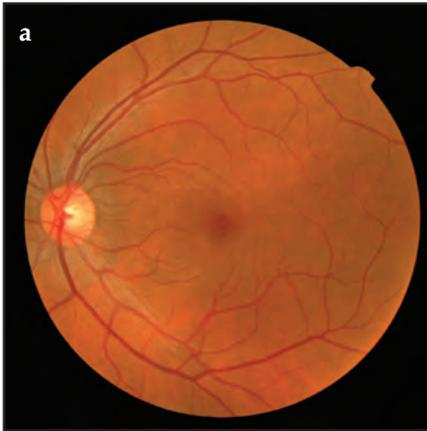


Figure 1a-b: Optical Coherence Tomography (OCT) of the Normal eye. **a)** The color photograph shows a normal macular reflex in a normal eye. **b)** OCT shows the depression appearance of the fovea in relation to the rest of the macula. We can observe the high reflectivity of the retinal pigment epithelium and the chorio capillaries (pink color structure). Opposite to this, there is a less precise appearance in the photoreceptor's area because of the poor return reflection effect (blue and black structure).

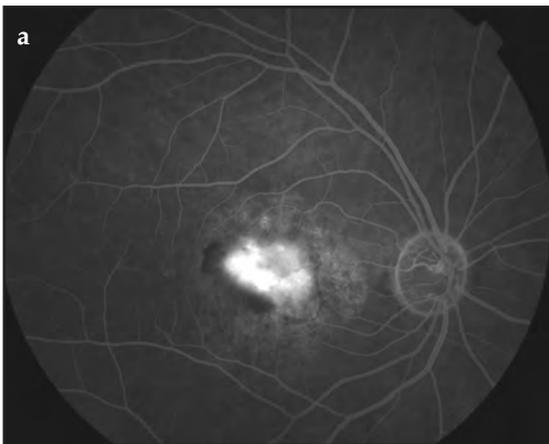
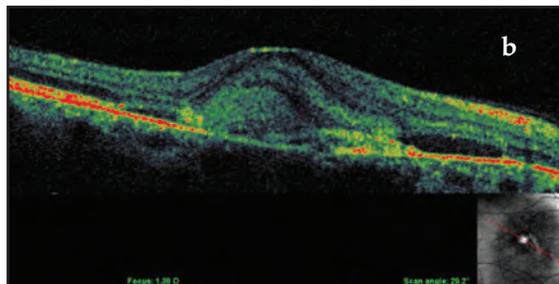


Figure 2ab: Choroidal Neovascularization in ARMD. **a)** Fluorescein angiography shows the late hyperfluorescence corresponding to the macular lesion. **b)** Optical Coherence Tomography (OCT) shows how neovascularization is causing a thickening of retina layers with presence of intraretinal fluid and little neuroepithelial detachment, confirming the activity of the lesion.



In Figure 1a-b we show the normal retina, for comparison with abnormal cases. Figure 2a-b shows alterations in age-related macular degeneration with choroidal neovascularization.

In Figure 3a-b we present central serous chorioretinopathy; in Figure 4a-b a severe non-proliferative retinopathy with macular edema. Figure 5a-b shows a central venous occlusion with cystoid macular edema.

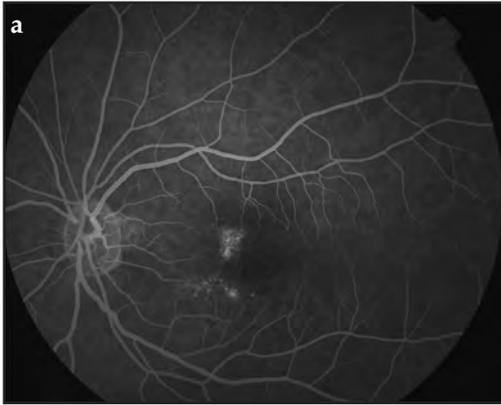


Figure 3a-b: Central Serous Chorioretinopathy. **a)** Fluorescein Angiography. We can observe hyperfluorescence in the areas of leakage of the macular pathology. **b)** Optical Coherence Tomography (OCT). A neuroepithelial detachment is clearly seen.

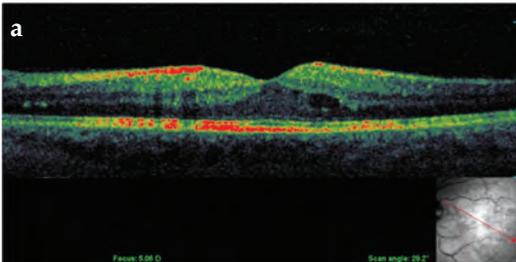
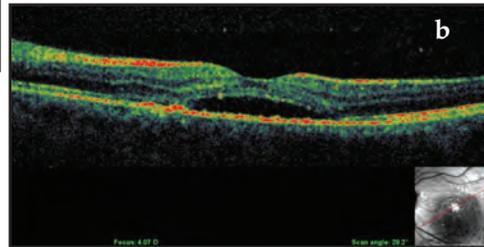
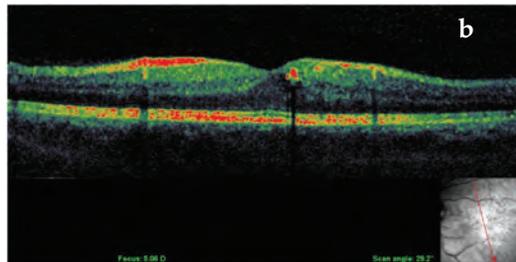


Figure 4a-b: Non-Proliferative Diabetic Retinopathy. With the help of Optical Coherence Tomography (OCT) we can observe the presence of little pseudocysts near to hard hyperreflective exudates secondary to the alterations of the macula in this stage of the retinopathy.



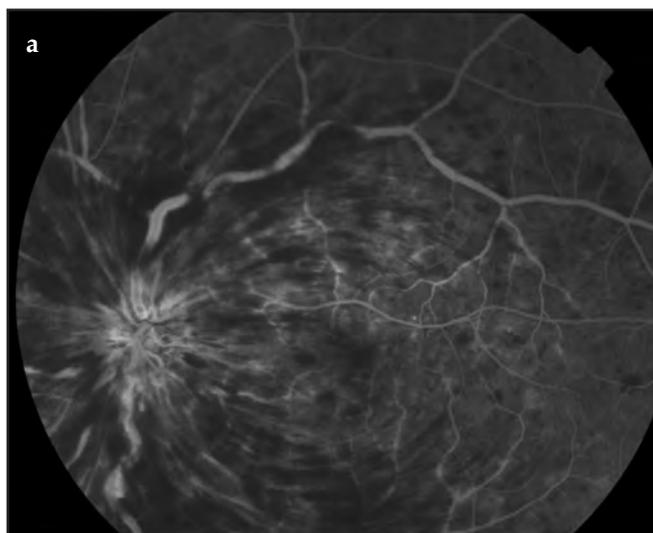
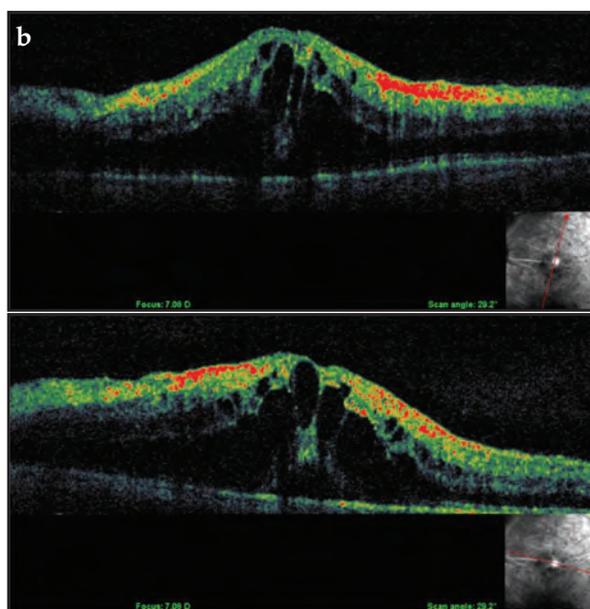


Figure 5a-b: Central Venous Occlusion with Cystoid Macular Edema. **a)** Fluorescein Angiography shows the presence of numerous retinal hemorrhages in the macular area, secondary to the venous occlusion. **b)** In these Optical Coherence Tomography (OCT) we can observe the presence of numerous intraretinal areas of high reflectivity, characteristic of hemorrhage and thick retinal layer tissue.





Current Clinical Application

Imaging of Anterior Segment Structures

This technology is also very helpful for the anterior segment surgeon, either the refractive or the cataract surgeon. The strongest reflected signals arise from epithelial surface of the cornea and the highly scattering sclera and the iris. Other clearly identifiable structure is anterior capsule of lens. Structures in the angle region like trabecular meshwork and canal of Schlemm are not clearly visualized in the tomogram since the incident and backscattered light is highly attenuated after traversing the overlying scleral tissue.

Glaucoma

Due to the OCT scan, the user can visualize the angle in multiple cross-sections of the anterior chamber. Because the OCT uses infrared light, the pupil does not constrict, providing a more natural view of the angle without changing its anatomy. A measuring tool can then be used to calculate a definitive angle depth in degrees. Now, patients at risk for angle-closure glaucoma may be monitored more closely as the crystalline lens matures.

Evaluation of RNFL in Glaucoma

Optical coherence tomography is one of the most reliable, reproducible and accurate methods of monitoring changes in the optic nerve and retinal nerve fiber layer (RNFL), which is imperative for diagnosis and management of early glaucoma (Figure 6). When used in

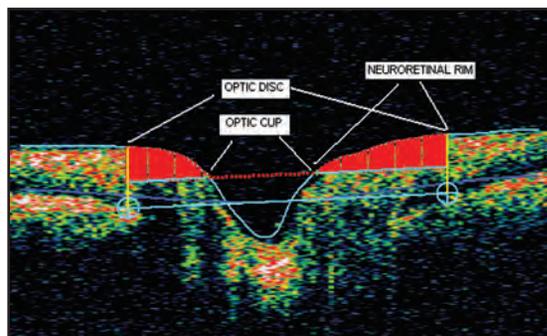


Figure 6: Optic nerve head scan on OCT showing a normal nerve head.

conjunction with regular clinical examinations with IOP measurements and periodic visual field testing, retinal tomography offers accurate assessment of the retinal nerve fiber layer integrity. Quantification of the peripapillary retinal nerve fiber layer (RNFL) thickness can provide clinicians with objective information about the optic nerve in different pathologic conditions. Several imaging techniques can be used to obtain such a measurement; most recently, optical coherence tomography (OCT) has demonstrated several merits. This technology has been used extensively to quantify RNFL thickness in atrophic diseases such as glaucoma, Leber hereditary optic neuropathy, traumatic optic neuropathy, and band atrophy.

Refractive Surgery Application

When applied to refractive evaluation the anterior segment OCT maps corneal thickness in 25 spots across the cornea and has great repeatability. It can also create a differential map to compare past readings and detect subtle changes involved in corneal-thinning



conditions. This can be very useful in following a patient with keratoconus or pellucid marginal degeneration. Even if the corneal topography is symmetric and central-ultrasound pachymetry is normal, the OCT pachymetry map can reveal an abnormal pattern of corneal thickness, raising suspicion for forme fruste keratoconus.

High-Resolution OCT Corneal Scan

Post LASIK procedures, high-resolution corneal scans detail the actual thickness of the flap and the residual stroma. This is useful in ensuring that enough residual stroma will remain after an enhancement.

Imaging of Abnormal Retinal Structures

OCT can effectively distinguish lesions that ophthalmoscopically are difficult to identify and resemble various stages of macular hole development like lamellar macular hole, macular cysts, macular edema, sub-retinal hemorrhages, retinal and/or foveal detachments of neurosensory

retina or pigment epithelium, and epiretinal membranes with macular pseudoholes.

Enhanced Visualization of Macular Holes

Comparing to biomicroscopical observations OCT gives additional information about idiopathic macular holes, especially in their early stage. According to the literature, the foveal cystoid space or pseudocyst is considered the first step of full-thickness macular hole formation, instead of foveolar detachment as proposed by Gass^(4,5). A foveal pseudocyst appears in the tomographic imaging as a large intraretinal cystoid formation that occupies the inner part of the foveola and disrupts the outer retinal layers. A foveal pseudocyst is considered a specific entity that may be the result of the incomplete separation of the vitreous cortex at the foveal center.

The role of the vitreous cortex in development of macular holes using OCT has also been clarified in various studies^(6,7) (Figure 7). But the greatest advances obtained by OCT are in the field of vitreo-retinal surgery.

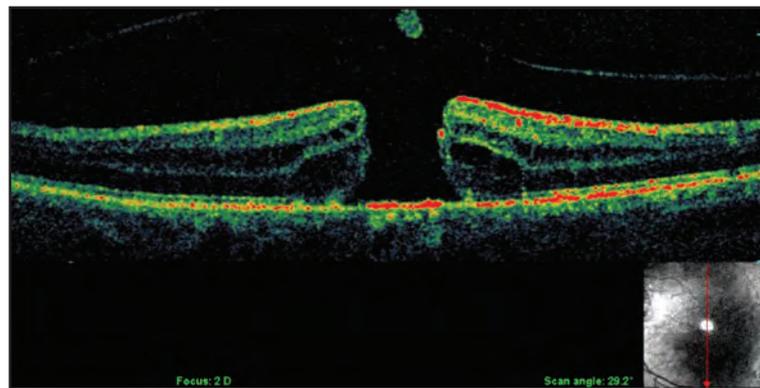


Figure 7: The OCT image shows a full thickness macular hole with a well evident vitreous operculum at its top.



Indeed the ability of OCT to more accurately identify macular holes allows clinicians to better predict the surgical outcome. OCT reveals anatomic configuration of surgically closed macular holes within 24 hours after successful surgery⁽⁸⁾.

Interesting results have been obtained by using OCT also in the study of retinoschisis, that is represented in the OCT as retinal splitting of the outer retinal layers in the macula, with inner retinal columnar structures that bridge the inner and outer retinal layers⁽⁹⁾.

OCT has demonstrated that foveal retinal detachment and retinoschisis are common in severely myopic patients, with posterior staphyloma, while biomicroscopic observation revealed only a retinal detachment. Retinal detachment may precede the formation of a macular hole in severely myopic eyes⁽¹⁰⁾.

Also, idiopathic posterior pole retinoschisis in highly myopic eyes is easily diagnosed by OCT and it is possible to establish the true extent of these macular changes⁽¹¹⁾.

In the presence of idiopathic macular membranes, OCT can give complementary information in the evaluation of anatomical features of the macula before and after surgical removal of the membrane.

The epiretinal membranes are identified by OCT when they are separated from the inner margin of the retina, and appear as a hyper-reflective thin band anterior to the retina. When they are tightly adherent to the retinal surface they are identifiable by an increased reflective image on the retina (Figure 8). OCT, in distinction from other diagnostic methods such as ultrasound, can detect the presence of hidden retinal alterations, such as a cystoid macular

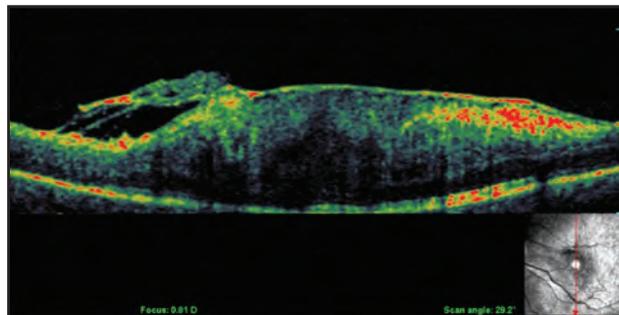


Figure 8: A reflective band is present just anterior to the neurosensory retina. A thickening of the neurosensory retina and diffuse macular edema is visible under the tractional epiretinal membrane.



edema or a sub-foveal retina detachment, or a tractional macular hole. OCT examination has demonstrated that the thickness of the macula decreases after epiretinal membrane surgery.

Application of OCT in Diabetic Retinopathy

Accurate longitudinal comparisons of serial OCT scans depends upon reproducibly locating the central fovea. In patients with central fixation each OCT scan is centered on the patient's fixation such that the OCT scan passes through the central fovea. In patients with eccentric or imperfect fixation, the location of the fovea can be estimated from each OCT scan using a computer algorithm that searches for a focal minimum in total intraretinal reflectivity which typically coincides with the central foveal depression.

OCT can be considered a sensitive technique in the study of diabetic retinopathy for the early detection of retinal abnormalities and in

quantifying macular thickness after laser treatment.^(12,13)

By OCT it is possible to differentiate between cystoid and diffuse edema. In cystoid edema, low reflective spaces, divided by thin hyperreflective membranes, correspond to cystic spaces in the outer plexiform and inner nuclear layers. A large central cyst was occasionally noted to extend beneath the inner limiting membrane. Intraretinal fluid accumulation causes reduced optical reflectivity. In diffuse edema, an area of low reflectivity was present within the retina.

Significant differences in retinal thickness comparing patients with diabetic retinopathy and normals have been detected by OCT, even in absence of clinically significant macular edema. Also an increase in macular thickness in diabetics either without retinopathy and/or edema compared to controls has been demonstrated^(14,15). OCT is also useful for evaluating and documenting macular edema and mapping it⁽¹⁶⁾ (Figures 9 and 10).

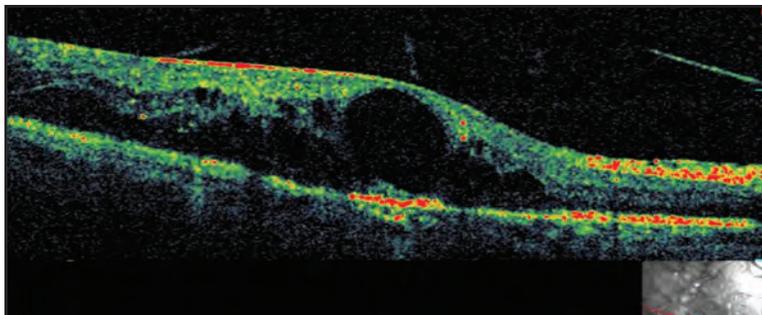


Figure 9: The tomography demonstrates a cystoid macular edema in a patient with diabetic retinopathy. The strict adherence of the surface of the inner retina layer with the vitreous band is also evident.

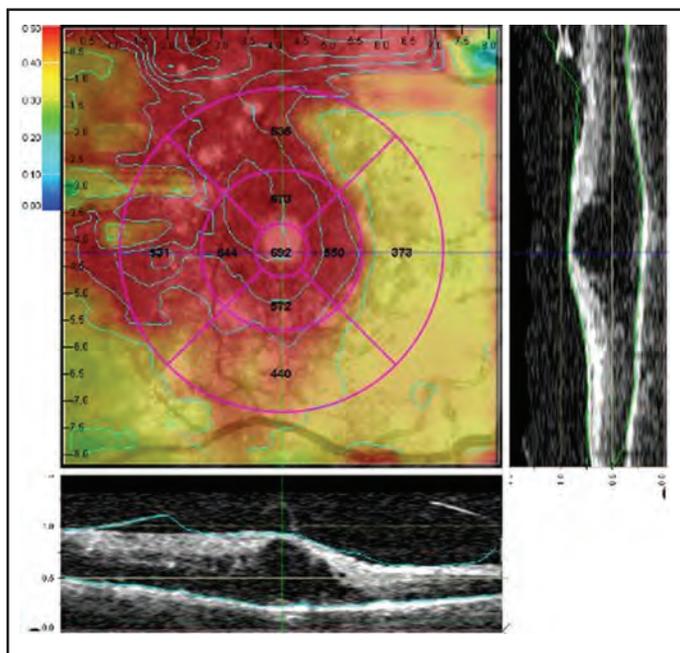


Figure 10: The map shows areas of thickening of the macula.

After vitreous surgery for diabetic macular edema, best-corrected visual acuity improvement is greater in eyes with less preoperative increase in thickness of the neurosensory retina⁽¹⁷⁾. Recently an OCT retinal thickness map has been developed to provide more precise measurements of macular edema⁽¹⁸⁾.

Age-related Macular Degeneration

Severe vision loss in this disease is the result of choroidal neovascular membrane formation. Choroidal neovascularization typically appears as either classic choroidal neovascularization (well delineated) or occult neovascularization (less well delineated).

A number of new pharmacologic approaches are being applied to macular degeneration. Vision loss in age-related macular degeneration typically results when choroidal neovascular tissue with or without concomitant hemorrhage and exudation into the fovea occur. The presence of hemorrhage, subretinal fluid or hard exudate under the fovea are usually detrimental to vision. The presence of choroidal neovascularization itself underneath the central fovea may likewise be detrimental to vision.

Optical coherence tomography, because of its high resolution capability, is able to image subretinal fluid, intraretinal thickening and sometimes choroidal neovascularization. As a result these capabilities, OCT may have utility in the assessment of new treatment modalities for age-related macular degeneration.



Cystoid Macular Edema (CME)

Ophthalmoscopically, CME appears as elevation or thickening of the central macula. Intra-retinal cyst formation is often present. The area of retinal elevation often has ill defined borders both on ophthalmoscopy and clinical examination. The presence of media opacity and/or a small pupil, as is common in uveitic patients, may make determination of the presence and area of CME difficult.

The use of optical coherence tomography for the measurement of cystoid macular edema may be useful. Longitudinal measurement of either axial scans and/or topographic images as described for diabetic macular edema can be utilized. Additionally, the amount of media opacity and pupillary miosis in patients with uveitis will not likely interfere significantly with the images obtained by optical coherence tomography.

Pathological Macular Disorders

In the presence of macular diseases, OCT has demonstrated several new findings that may help the interpretation of the pathophysiologic changes in various disorders.

In idiopathic juxtafoveolar retinal telangiectasis, OCT shows a hyperreflective band within the inner retina, and has demonstrated the presence of a small plaque, consistent with the hypothesis of Gass and Blodi, of an epithelial proliferation into the inner retina in some cases of retinal telangiectasis⁽¹⁹⁾.

In idiopathic polypoidal choroidal vasculopathy, OCT has demonstrated a serosanguineous detachment of the retinal pigment epithelium, suggesting that these lesions are situated beneath Bruch's membrane and are covered anteriorly by both retinal pigment epithelium and Bruch's membrane⁽²⁰⁾.

OCT is useful to establish the presence of cystic degeneration of the macula, when macular modifications are not noted clearly on biomicroscopic examination or fluorescein angiography, in patients with initial central serous chorioretinopathy, in patients with no specific serous retinal detachment, and in inflammatory diseases.

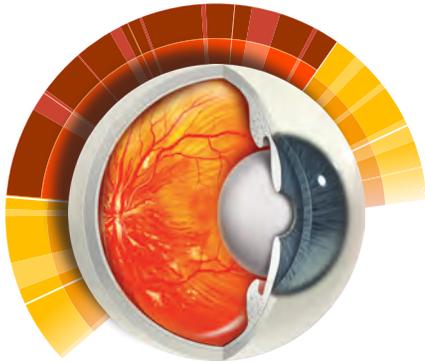
With recent advances in technology, a new generation of OCT devices is now being developed. This new OCT technology may achieve "in vivo" retinal imaging with less than 3 μm axial resolution. A higher longitudinal resolution may contribute to a better visualization of intraretinal structures and pathology and could increase the reproducibility, sensitivity and specificity for diagnosis of retinal and macular diseases.

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4

Optical Systems for Ocular Diagnosis and Vitreoretinal Surgery

SAMUEL BOYD, MD

General Considerations

Examination of the fundus is increasingly important. The sophisticated methods available today provide great accuracy and significant information. Retinal exams may reveal the presence of vitreous and retinal diseases and even contribute to the detection of non-ocular diseases. Many systemic diseases can affect the anterior-posterior segments. Since the blood vessels of the retina are observed during the examination, certain systemic problems may be uncovered (e.g., high blood pressure or diabetes).

The need for frequency of eye exams generally differs with age and retinal diagnosis. A child with no symptoms should have an eye exam at age three. Early observation is important because permanent decrease in vision (e.g., amblyopia) can occur if not treated early, usually by ages 3-5. Some pa-

tients have moderate to high risk factors for eye disease (e.g., people with diabetes or a family history of eye disease) and may need more frequent checkups. Also, if older children have trouble in school, encounter problems with reading, or tend to rub their eyes when reading, a complete eye exam with retinal fundus observation may be necessary sooner. These observations are best accomplished after dilating the pupils and utilizing the indirect ophthalmoscope.

Completing the Evaluation with Additional Tests

In addition to direct and/or binocular indirect ophthalmoscopy, other techniques of examination may be indicated such as slit-lamp indirect ophthalmoscopy (condensed lens), color tests, retinal fluorescein and indocyanine angiograms, ultrasonography, and OCT.



Observation of the Fundus

This observation includes but is not limited to the retina, blood vessels, and optic nerve. The optic nerve can be checked for swelling, neuritis, drusen or other problems. The blood vessels can be viewed for combined problems between retina and macula such as occlusions, hemorrhages, or neovascularization.¹

Evaluation of the Central Retina

In general, this evaluation is aimed to detect diabetic macular retinopathy, macular degeneration, and choroidal neovascularization (CNV) as well as other abnormalities of the retina, macula, optic nerve, and rare intraocular tumors. However, for cataract surgery candidates, preoperative evaluation of the macula is of particular relevance for establishing the cataract as the only cause of the patient's poor vision.

Patient's expectations for vision after cataract surgery are high, and the most common reason why patients do not see well after these procedures is macular dysfunction. Therefore, preoperative evaluation for pre-existing macular pathology is critical to allow detection of treatable disease or to inform patients that they may have a guarded visual prognosis (Figure 1).



Figure 1: Close-up Observation of the Macula. Careful biomicroscopic examination of the macula with the macula lens (inset) or the 3-4 mirror lens may reveal blood, macular thickening, an abnormal reflex or intraretinal spaces (edema) that may not be clearly detected by indirect ophthalmoscopy.

Choroidal neovascularization located underneath the center of the fovea is the leading cause of legal blindness in the United States. Since the associated changes in the macula may be subtle, ophthalmologists should be cautious about overlooking them if the retina is examined quickly through a nondilated pupil.



Using video camera operating characteristics optimized for low light level imaging, non-mydratic stereoscopic digital video retinal images provide substantial agreement with accepted "gold standard" ETDRS 35mm stereo fundus photography for retinal pathology diagnosis and excellent agreement for recommended retinal examination follow-up.²

At present, dilated indirect ophthalmoscopy coupled with stereoscopic examination of the macula using slit lamp biomicroscopy remains the gold standard for rapid screening of the retina in the comprehensive ophthalmologist's office.

Slit-Lamp Biomicroscopy and Indirect Ophthalmoscopy Using Condensing Lenses

During ophthalmoscopic exam with direct visualization (direct ophthalmoscope), small lesions or degenerations may be difficult to identify, especially because of their size, characteristics, and location.

With the help of small condensing (ie: 78 dp) lenses and the slit-lamp, the physician may obtain a real inverted and stereoscopic image with a wide field and an excellent resolution of the observed retina.

For this specialized observation different types of condensed lenses can be used, including the +90 dp, +78 dp, +60 dp, the super pupil lens (+135 dp), or the superfield lens. Although it is not necessary to dilate the

patient's eye for this observation, the most recommended lens is the +90 dp or the super pupil lens (Figure 2).



Figure 2: Indirect Close-up Observation of the Posterior Pole. This revolutionary technique is a significant contribution to the anterior and posterior segment surgeon. With the 78 dp or 90 dp lens (inset) you may observe the posterior pole and macula in a general view without the need to dilate the patient's pupil. With this kind of lenses, however, the ophthalmologist can not appreciate pathological alterations in detail as can be viewed with the lenses described in Figure 1.



Recommended Method

- 1). Low-to-moderate intensity of light is recommended, and the beam should be adjusted to a width between 3mm and 4 mm. The light beam will be perpendicular and with an inclination between the grades of 0 – 10.
- 2). Hold the lens at a distance of approximately 8 mm from the patient's eye, almost touching the eyelashes. Once the retina is in focus, then the light beam intensity can be increased, or slit-lamp filters can be changed for a better contrast observation.
- 3). If the physician is interested in a specific area of the retina, the patient can be asked to follow the fixation target. The hand can be moved to look for the desired point.
- 4). The less lens potency in diopters, the greater the distance between the lens and the patient's eye needed to observe the retina. For a comfortable distance and a good observation of the retina most times the +90 D lens is recommended.

The presence and depth of several alterations like subretinal fluid can be more effectively detected and evaluated using this method.

SCREENING METHODS

Non Mydriatic Digitized Video Retinal Imaging (NMDV)

The NMDV retinal images are taken in stereoscopic digital 35mm 30°, 7 standard-field retinal photographs. Stereo pairs are obtained from the posterior pole, nasal, superior, inferior, temporal, and the optic disc. Following pupil dilation, 35mm photography is performed. Using an appropriately validated digital video imaging system, optimized for low light level imaging, and associated validated grading protocols, the NMDV system can be used to assess diabetic retinopathy, macular diseases, and other clinical conditions. This technology allows for follow-up by facilitating remote access of patients into an eye care program aimed at managing retinal eye disease.

Digital fundus photographs as well as the retinal angiogram pictures sequence have the advantage that they can be taken at minimal cost and inconvenience to the patient and can be transmitted by electronic mail through the Internet to distant experts, for consultation web or presentations.¹

Ultrasound B

Ultrasound imaging equipment (type B), allows retina specialists to «see» the eye in great detail without the pain and risk of exploratory surgery, or the limitations and uncertainty inherent in traditional visual examination. Ultrasound is used to detect and diagnose many eye diseases (retinal detachments, vitreous hemorrhages) and injuries (intraocular foreign bodies), to measure the eye prior to corrective surgery, and directly as a treatment tool (Figure 3).

Purpose of the Ultrasound B

An ophthalmologist uses ultrasonic imaging to help diagnose the underlying cause(s) of a patient's symptoms, to assess the general condition of an injured eye, and to evaluate the eye prior to surgery. Situations that may call for ultrasonic imaging include:

- 1). *Excessive tearing or visible infection.* These external symptoms could indicate a serious underlying problem such as a tumor, an internal infection, the presence of a deeply

Figure 3: B-Scan Ultrasound for Detection of Vitreoretinal Diseases. The B-scan ultrasound computerized technology helps surgeons detect vitreoretinal diseases such as retinal detachments, vitreoretinal tractions, vitreous hemorrhages and luxated crystalline lenses or intraocular lenses. In this B-scan picture you may observe a large retinal detachment with traction over the central visual axis (arrow).





lodged irritant (foreign body), or the effects of a previously unrecognized injury. When a patient presents with general symptoms, ultrasound can speed diagnosis if a serious condition is suspected.

- 2). *Impaired vision.* Fuzzy vision, poor night vision, restricted (tunnel) vision, blind spots, extreme light sensitivity, and even blindness can all stem from inner eye conditions ranging from glaucoma and cataracts, to retinitis, detached retina, tumors, or impaired blood circulation.
- 3). *Eye trauma.* The eye can be damaged by a direct impact or a puncture wound, as a result of a general head trauma, or by

intense light exposure. Even when the cause of injury is obvious, ultrasound can reveal the exact type, extent, and location of damage, from deformations and ruptures to internal bleeding, and help guide emergency care efforts.

Importance of Binocular Indirect Ophthalmoscopy

An important era began in the late 1940's, when Charles Schepens introduced the binocular indirect ophthalmoscope (Figures 4 A-K). It is, by far, the most valuable instrument available for evaluation of the detached retina and other pathologies of the

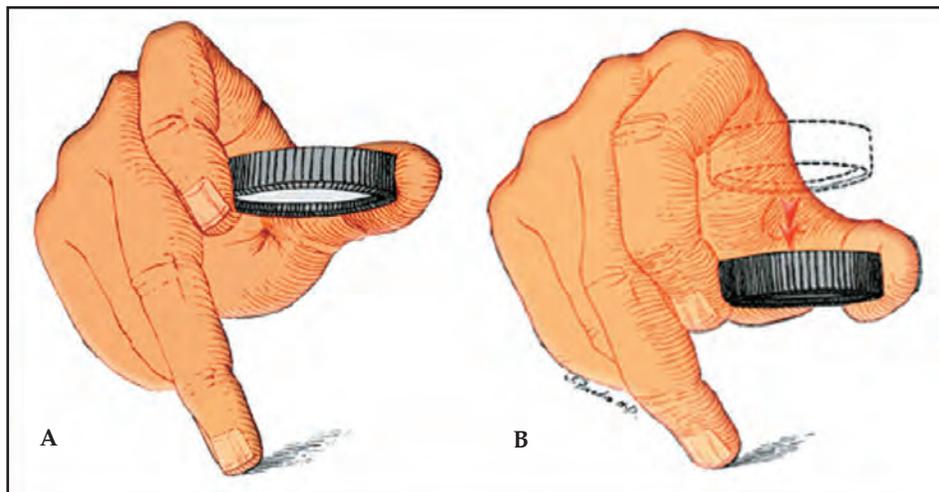


Figure 4 A-B: Precise Way to Hold Condensing Lens. Figure **A** shows how the lens is grasped between ball of thumb and tip of index finger. In Figure **B** you may observe when the wrist is extended, and third finger is extended as pivot. Manner in which lens is moved closer to or away from eye is shown.



Figure 4C: Examining the Patient's Left Eye. Examiner is observing superonasal quadrant of patient's left eye fundus. He stands to left of patient, and third finger of left hand controls lower lid. Right hand controls head, and thumb of right hand controls upper lid. To observe temporal half of left fundus, examiner should stand on right side of patient. Left third finger then controls upper lid, and right thumb retracts lower lid.



Figure 4D: Examining the Patient's Right Eye. Observer is standing on left side of patient, examining superior retina, and is shown holding lens in his left hand. Thumb and index finger control lens, and third finger simultaneously retracts lower lid. Right hand is used to control patient's head, and thumb of this hand retracts upper lid. These hand positions permit examination of entire temporal half of right fundus. To observe nasal half, examiner should stand on right side of patient. Left third finger will now be used to hold upper lid, and right thumb now retracts lower lid. Considerable movement of examiner's body and head will be necessary to see entire fundus.



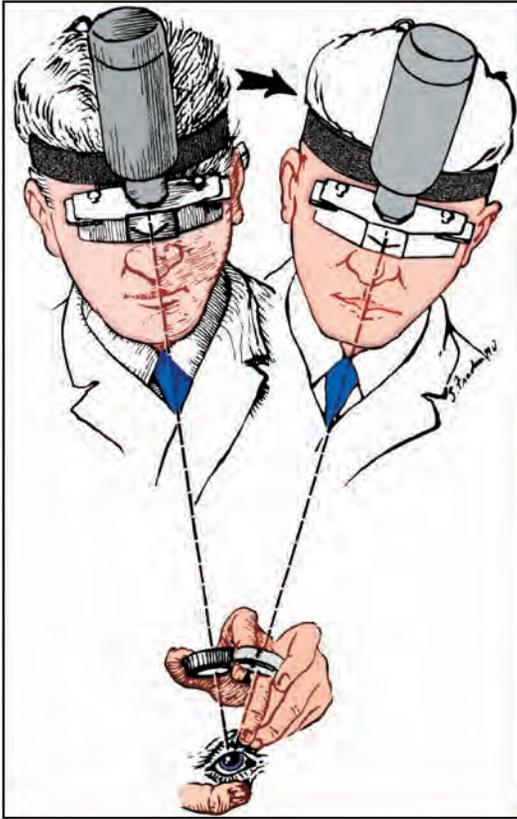


Figure 4E: Coordinated Movement of Observer's Head and Tilting of Lens. The coordinated movement of the observer's head and the tilting of the lens is a maneuver that takes considerable practice. The head is not moved on the neck but, rather, the whole torso is moved from side to side and forward and backward while the lens is appropriately tilted. It is essential to practice this maneuver until it is completely natural and automatic.

Axis is formed by examiner's visual axis (split by prisms in headpiece), condensing lens, patient's pupil, and area of fundus under study. Fulcrum of this axis is patient's pupil (Figure 4F). In order to observe another part of fundus, observer's head must move and lens tilt in such way that new axis also has its fulcrum in pupil.

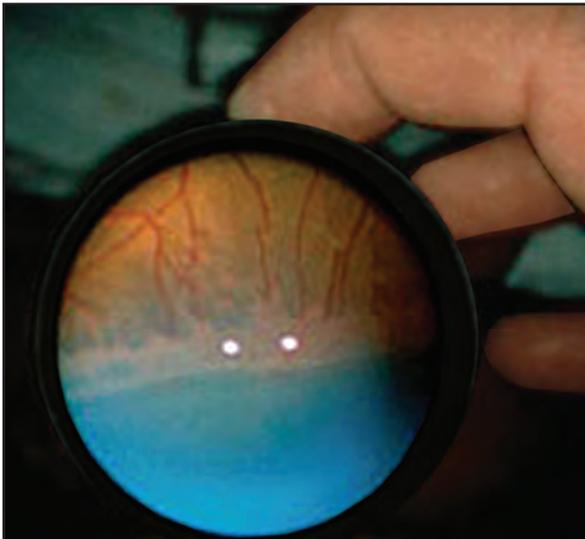


Figure 4F: Enables view of fundus through cloudy media or around partial intraocular opacities. Excellent survey technique allowing large field of view. Allows easier examination of peripheral fundus than direct ophthalmoscopy. Facilitates determination of fundus depressions and elevations. Fundus examination is faster and comparison between eyes is easier. A supplemental mirror can be attached to many binocular indirect models, permitting simultaneous visualization by examiner, student, colleague or client.



Figure 4G: Drawing of Fundus - Relationship of Fundus Chart to Patient's Eye. Chart is used, inverted, for a precise drawing of the retina. The 12 o'clock position on chart corresponds to the 6 o'clock position of patient's eye. Likewise, the 6 o'clock position on chart corresponds to 12 o'clock position on patient's eye. When the fundus is viewed through the condensing lens (20 dp), the inverted image seen through the lens will exactly correspond to the orientation of chart. The information in lens image can be directly drawn on inverted chart.

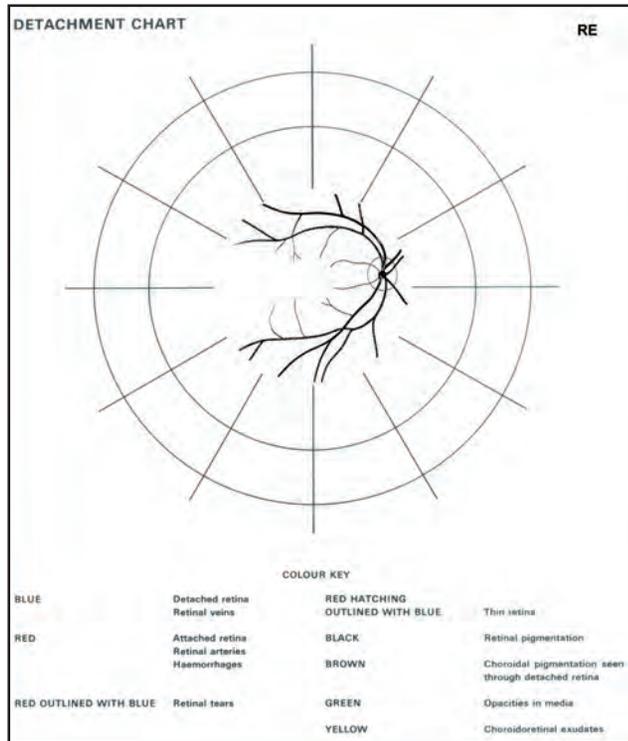


Figure 4H: Fundus Image Inverted. The fundus image in the condensing lens is completely inverted; that is, the image is upside down and also backwards as regards right and left. Left eye is being examined (inset). In drawing this image, it should be copied just as seen on inverted drawing chart, thus preserving normal relationships. If you look up and temporal in the patient's eye, since the image is inverted, do you see the lower nasal part of the fundus? The answer is NO. You always see the areas which you are looking at. However, whatever field you see in the condensing lens will be inverted.

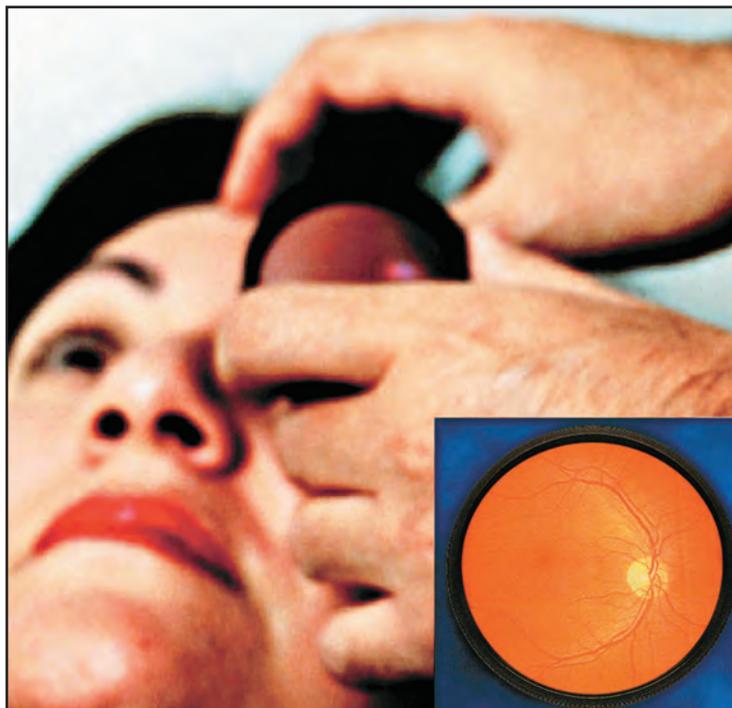




Figure 4I: Scleral Depression. Showing depressor being applied to patient's eye, with patient looking down. When patient looks up and depressor is introduced, examiner will be in position to see superonasal periphery.

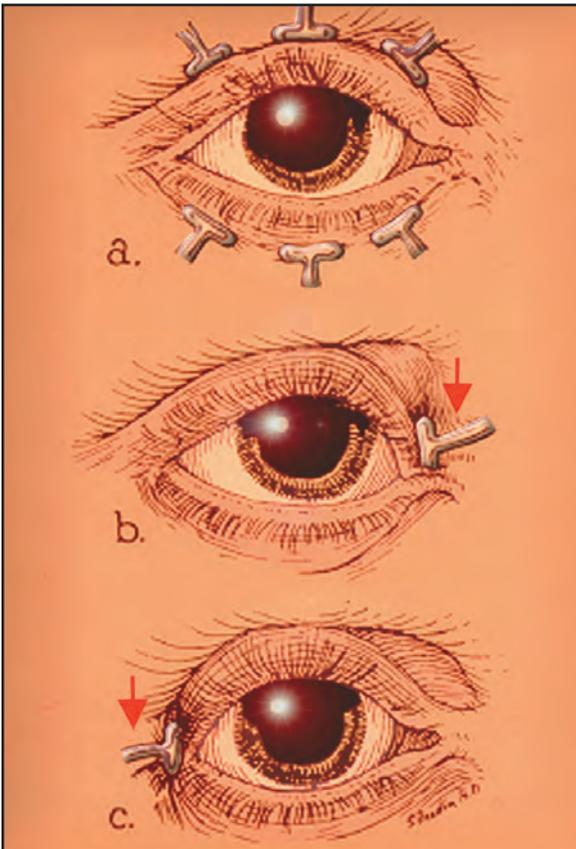


Figure 4J: Performing Scleral Depression Through the Lids. Figure a, shows the approximately six positions of depressor on lids, sufficient to provide view of entire periphery with exception of 9 and 3 o'clock positions. Figure b, shows how, in most patients, it is possible to drag upper lid down enough to visualize nasal horizontal meridian. Figure c, shows how it is usually possible to drag upper lid down enough to examine temporal horizontal meridian.



Figure 4K: Lateral View of Indirect Ophthalmoscopy. This side view shows a right eye observation of the retina. A proper pupil dilatation will help the surgeon through the complete preoperative evaluation of the retina including periphery. Since retinal detachments may present with different characteristics as peripheral degenerations and tears even in different quadrants, is imperative to observe every detail along the four quadrants of the retina.



retina and vitreous. The current high rate of reattachment is due not only to improvements in surgical technique but also to improved methods of ocular examination. Additional important information is obtained with the Goldmann three-mirror lens.

Lasers for Early Detection of Retinal Disease

Early detection and treatment of retinal disease can dramatically improve patients' prognosis. The advent of new laser technology is helping ophthalmologists to identify and chart structural change in this light-sensitive membrane from the earliest stages. Conventional or direct ophthalmoscopy gives good two-dimensional images of the retina, revealing changes to the surface of the membrane that may indicate various disorders.

In cases of diabetic retinopathy, for example, blood vessels begin to leak, and the retina thickens—sometimes before the patient notices any visual impairment or other symptoms.

However, this conventional method of examining the retina does not enable the clinician to quantify the structural changes identified. The challenge of recent years has been to find ways to view the retina stereoscopically and to measure the pathology seen so that the diagnosis and monitoring of disease, and response to treatment, may become much more accurate.³

The advent of technologies such as the scanning laser ophthalmoscope promises a much deeper understanding of retinal pathology and more accurate assessment of effective treatment options.



Scanning Laser Ophthalmoscope (SLO)

The scanning laser ophthalmoscope generates a succession of three-dimensional computer images of the retina, enabling the operator to create a topographic map of the membrane and its contours.

The Scanning Laser Ophthalmoscope (SLO) was invented by Webb, Pomeranzeff, and Hughes in 1979. It used a very narrow moving beam of light which could bypass most ocular media opacities (i.e. corneal scars, cataracts, vitreous hemorrhage) to reach the surface of the retina and record its surface detail. A live video image of the retina was displayed on a computer monitor and test results were digitally recorded. Several diagnostic tests were possible with this machine.^{4,5}

Conventional fundus imaging using a fundus camera produces color fundus pictures. The scanning laser ophthalmoscope (SLO) has the advantages of lower levels of light exposure, improved contrast, and direct digital imaging. The background fundus and retinal vasculature have similar appearances with the two imaging modalities. Internal limiting membrane reflections are prominent with the SLO. Identification of new vessels in the diabetic fundus is easier with the SLO than with color fundus photographs. A color SLO offers all the advantages of the present monochromatic imaging system with the added advantage of true color representation of the fundus

SLO microperimetry might be effective for quantitative assessment of retinal sensitivity in retinal scars and for detecting fixation points and determining their stability.

Scanning laser ophthalmoscopy is a retinal imaging technique that is based on the standard scanning laser microscope. The important difference is that in scanning laser ophthalmoscopy, the optics of the eye serve as the objective lens. Scanning laser ophthalmoscopes and microscopes, when equipped with a confocal aperture, offer fundamentally better performance than conventional imaging instruments. The confocal SLO generates high contrast images and can do optical slicing through weakly scattering media, making it ideal for imaging the multilayered retina.

Wide Angle Fundus Observation System for Vitreoretinal Surgery

Fundus visualization during entire vitreoretinal surgery is a must especially while operating complicated cases.

Proper visualisation of posterior pole and periphery helps surgeon to perform difficult steps with safety and efficacy and also avoid unwanted complications.

For this purpose non-contact wide angle observation systems like BIOM and EIBOS are ideal.⁶



The wide angle viewing system currently include:

-The BIOM noncontact system with a field of view of 70°, 90° or 110°.

-The EIBOS noncontact system with a field of view of 100° for 90 – diopter and 125° for 60 – diopter.

-The VOLK reinverting operating lens system (ROLS); can be used to visualize up to vitreous base and ora serrata.

Wide angle viewing systems can be used in cases of retained lens mater and removal of displaced intraocular lens as surgery at the posterior pole as well as proper inspection of the periphery of the fundus is possible using the same viewing system. In cases of diabetic patients, panretinal photocoagulation, dissection of tightly adherent membranes and gas fluid exchange are all facilitated. While working in one area, remote traction with impending development of tears or haemorrhage can be visualised in phakic, aphakic and pseudophakic patients. Surgical procedures like dissection of anterior proliferative vitreoretinopathy, gas fluid exchanges and silicone oil installation both a gas – silicone oil exchange as well as perfluorocarbon liquid silicone exchange can be performed with the same viewing system maintaining proper focus of the desired area.

Surgery for retinopathy of prematurity is best performed using the noncontact systems,

because of the decreased scleral rigidity of the infant eye and the small size of the cornea with a steep corneal curvature.⁷

Optical Coherent Tomography (OCT)

With the optical coherence tomography (OCT), the patterns generated by the reflection of laser beams are used to build a cross-sectional image of the retina. OCT is an excellent tool for detecting submacular abnormalities, monitoring macular holes, and guiding laser treatment.⁸

With OCT, the macula is scanned and 600 scan points are achieved. The scan points are displayed as a retinal thickness map. This technique has allowed investigators to determine that the normal central retinal thickness is 150 mm.

In patients with an epiretinal membrane and macular edema, for example, OCT provides a unique, cross-sectional view of the retina that is not available with other techniques.

Conclusion

Such modern technologies offer great potential benefits to both patients and clinicians. They dramatically increase the scope for early detection and treatment of several vitreoretinal diseases.



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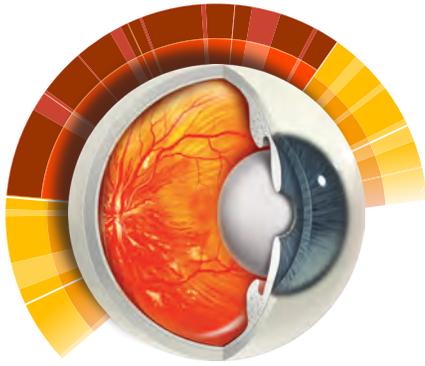
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5

Wide Angle Viewing Systems for Vitreoretinal Surgery

SHUNSUKE OSAWA, MD.,
YOSHIHIDE NAKAI, MD.

Wide-angle viewing systems are very important in vitreoretinal surgery. The use of these systems enables simultaneous observation of a wide area of an ocular fundus, thereby making it possible to accurately view a vitreoretinal state during surgery. Therefore, safe and comfortable surgery is possible by making good use of this system. In this chapter, we describe mainly how to use wide-angle viewing and its merits.

Introduction

In vitreoretinal surgery, it is extremely important to be able to see well an ocular fundus during surgery, and consequently a variety of surgical devices and lenses for observation of the fundus have been developed.

Lenses that have been used frequently in methods of observing the fundus since

the early years of vitreoretinal surgery are plano-concave lenses having a planar upper surface and a concave lower surface corresponding to the corneal radius of curvature. Plano-concave lenses provide a sharp observed image, and the magnification percentage is high. However, the visual field of observation is narrow, and only the central part of the fundus can be observed; as result, the upper surface is used as prism to observe the peripheral part of the fundus.

In addition, lenses such as a magnifying lens whose upper surface is convex to magnify and observe the central part of the fundus and a lens with both surfaces concave for fluid-air exchange should be replaced frequently during operation. Further, in cases of small pupils or corneal opacity, the observation of the fundus is difficult.

With wide-angle viewing systems described in this chapter, a wide range



of the ocular fundus can be viewed during surgery. It is possible to view an entire image of the fundus whose state changes from moment to moment during surgery, thereby enabling safe and comfortable surgery.

In addition, a wide visual field can be achieved even for small pupils, and it is not necessary to replace lenses at the time of fluid-air exchange and air-silicone oil exchange. In addition, laser photocoagulation in the extreme peripheral region can be performed under scleral compression.

Types and Outline of Wide-Angle Viewing Systems

As wide-angle viewing systems, there are contact lens-type (contact-type) used by being placed on the cornea and non-contact type for observation with the convex lens kept at a position 5-10 mm away from the cornea.

Contact Lens-Type (Contact-Type)

This type is used by being placed on the cornea with the use of a lens ring sewed on the corneal limbus. There are various kinds.^{1,2,3} We mention currently typical products: Mini Quad and ClariVIT.

With Mini Quad (Mini Quad SSV ACS; Volk Optical Inc., Mentor, OH, USA) (Figure 1), the ocular fundus can be observed up to 127°. The observation is possible up to the ora serrata, and fluid-air exchange is also possible without replacing lenses. Under air perfusion, the observation is possible up to the pars-plana. ClariVIT (ClariVIT Wide Angle; Volk Optical Inc., Mentor, OH, USA) does not have a brim that Mini Quad has, and the head of the lens is cut (Figure 2). The cut design can prevent contacts of surgical devices, so that the scleral wound can be viewed within the visual field of microscope.

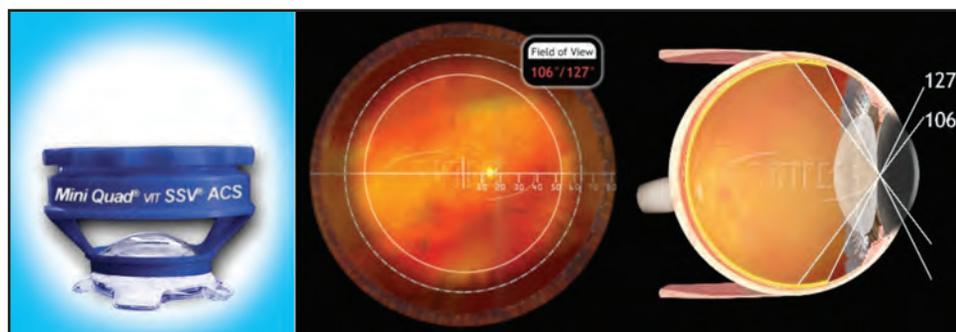


Figure 1. Mini Quad lens can observe up to 127°.

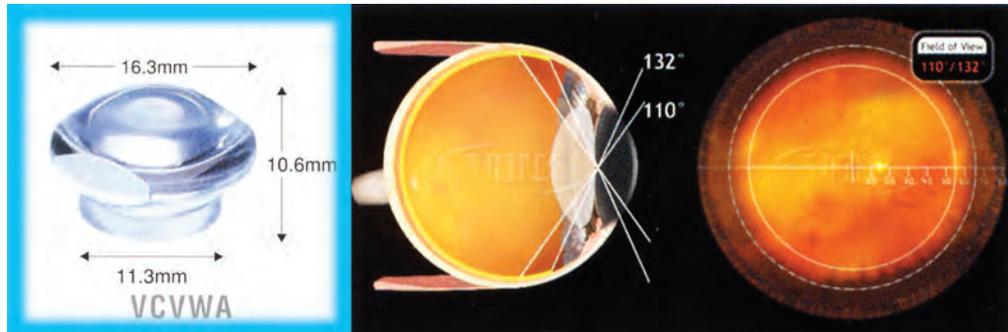


Figure 2. ClariVIT lens can observe up to 132°.

Both Mini Quad and ClariVIT produce an indirect image, so the inversion of the image is necessary. For the inversion of the image during surgery, SDI or Inverter tube is used. Table 1 shows comparison between

SDI (SDI: Stereoscopic Diagonal Inverter: Oculus, Lynnwood, Washington, USA) and Inverter tube (Inverter tube; Carl Zeiss Surgical GmbH, Oberkochen, Germany).

Table 1. Comparison SDI and Inverter Tube

	SDI	Inverter Tube
Image quality	Roof prism is added, so the image quality is deteriorated.	The prism in the lens tube is rotated, so the image quality is not deteriorated.
Working distance	Longer	Unchanged
Position of operator	Unnatural position	Natural position
ON/OFF switch	Electrical	Manual
Desorption during cataract surgery	Occasional desorption is necessary	Desorption is not necessary.
Image to the camera	Direct image	Indirect image



With SDI, the observed image quality is deteriorated by the addition of roof prism, and occasionally desorption is necessary during cataract surgery.

Inverter tube is completely embedded in the lens tube so that the working distance does not increase, and it is not necessary to take an unnatural position during surgery.

Non-Contact Type

This type employs a similar method of viewing the ocular fundus by using a prefix lens in the slit-lamp microscope. Currently typical products include BIOM (Binocular Indirect Ophthalmoscope, Oculus Lynnwood,

Washington, USA -Figure 3) and OFFISS (Optical Fiber-Free Intravitreal Surgery System, Topcon, Tokyo, Japan). It is difficult to conduct surgical manipulations by viewing an indirect image as it is; therefore, the inversion of the image is necessary. Similarly to contact lens-type (contact-type) systems, surgery is performed by setting SDI or Inverter tube on the surgical microscope to invert the image. BIOM and OFFISS are explained below.

BIOM

Characteristics: An entire image of the ocular fundus can be seen during surgery without contact with the cornea. For rhegmatogenous retinal detachment, the break



Figure 3. BIOM System.



region can be treated while checking the macular region. Also, when posterior vitreous detachment is prepared, it is possible to see the moment when a peripheral break is made, so a new break will not be missed. During fluid-air exchange and peripheral intraocular photocoagulation/freezing, it is not necessary to replace lenses, so that the overall visibility is improved, the safety can be secured, and the surgery time can be shortened. It is also useful for cases with opacity of the optic media and cases with small pupils.

Actual Use: To prevent dryness of the cornea, dispersive ophthalmic visco surgical devices are applied, and a small amount of BSS is placed thereon. First, the magnification of the surgical microscope is minimized. Next, the height of the surgical microscope is adjusted to bring the front lens at around 2-3 cm above the cornea of the patient.

The focus of BIOM is adjusted onto the device inserted into the eye or onto the retina. Next, the foot switch for the focus of the surgical microscope is lowered to adjust the front lens at around 1 cm above the cornea. The closer the cornea is, the wider the observation field becomes, but the front lens comes into contact with the cornea, and the lens is clouded due to the patient's body temperature during surgery.

For the observation of the retinal peripheral region, the eyeball is rotated in the direction where the operator wants to see. X and Y of the microscope only have to be moved in

the direction to which the eyeball is rotated. This corresponds to the sense of the ordinary movement from the ergonomic standpoint, and accordingly the surgery is easy.

With contact lens-type (contact-type) systems, the ocular fundus cannot be seen when the eyeball is rotated. In addition, the directions of X and Y are opposite. For example, when the operator wants to see the right part, it is necessary to move the microscope to the left. This manipulation is opposite to the ordinary movement, and accordingly the operation is difficult.

During fluid-air exchange, water drops are easily adhered onto the front lens, so the manipulation is done a little distance away from the cornea. The device is inserted from the scleral wound under direct vision or, while viewing the wound through the front lens with the lens tube of the microscope lifted up, but it is easy to insert the device through 23G/25G trocar.

OFFISS

Characteristics: These instruments have proven to be of value, especially in complex cases such as eyes with difficult preretinal membranes and with small pupils.

An Optical fiber-free intravitreal surgery system (OFFISS) has been developed to facilitate the use of bimanual technique during vitreoretinal surgery with the 40-diopter



(D) lens.⁴ In addition, OFFISS has been developed for non-contact wide-angle vitreoretinal surgery with the 120-D lens. In this chapter we describe the wide-angle viewing system: OFFISS, 120-D lens, for vitreoretinal surgery.

This wide-angle viewing system consists of a 120-D aspheric lens and a prismatic inverting optical system (Figure 4). The 120-D aspheric lens is used as a field lens. It is attached to the microscope (OMS-800; Topcon, Tokyo, Japan), and vertical motion can be done by foot switch of microscope (Figure 5). The lens swings into place between the objective lens and the cornea,

and the microscope-mounted inverting device (SDI: Stereoscopic Diagonal Inverter) automatically erects the inverted image of OFFISS, 120-D (Figure 6).⁵ The characteristic of OFFISS is that the position of field lens doesn't change even if the microscope moves to focus, because it can independently move field lens and the microscope.

Actual Use: The 120-D lens was located about 5 mm above the cornea, where the fundus was clearly and widely visible. This rarely interfered with the surgeon's manipulation of the micro-instruments for vitreoretinal surgery. To prevent dehydration of the corneal surface, the cornea was moistened with



Figure 4: OFFISS, 120-D lens (OMS-800)



Figure 5: Foot switch of OFFISS (*); vertical motion switch.

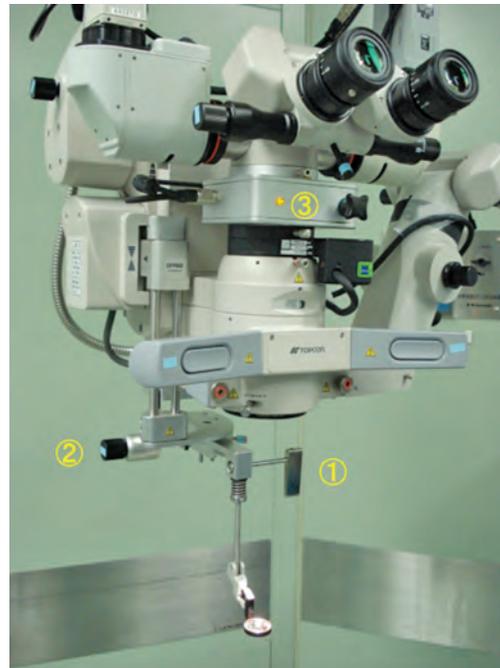


Figure 6: The lever (1) is knocked down and the dial (2) is turned, the lens can be swung into place between the objective lens of the microscope and the cornea. The fundus image is automatically inverted with SDI (3).



dispersive ophthalmic viscosurgical devices, and aspirating speculum was very useful to prevent cloudiness by the dew condensation of the 120-D lens (Figure 7).

With the OFFISS, 120-D lens, the surgeon can practically see the entire fundus clearly. The field of view (over 130 degrees, Figure 8) is the same as the wide-angle contact lens (ClariVIT, MiniQuad, etc), and it almost observes the ora serrata (Figure 9).⁶ This system maintained a good view through a small pupil even when the vitreous cavity was filled with gas by fluid-air exchange.

Discussion

The Comparison with other wide-angle viewing systems confirms a very similar most wide field of view (Table 2).⁷ Furthermore, noncontact viewing systems have advantage over contact wide-angle viewing systems in that they avoid wicking or trapping blood between the lens and the cornea. This minimizes lost operation time for vitreoretinal surgery from cleaning the visual path.^{8,9}

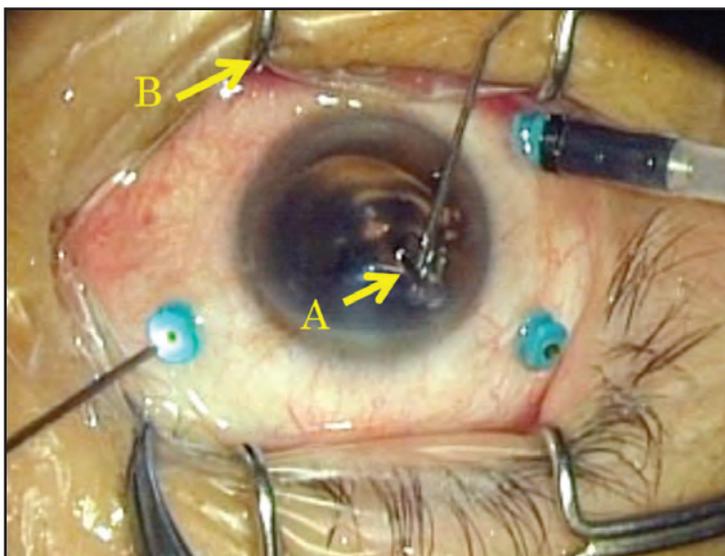


Figure 7: A) The cornea was moistened with dispersive ophthalmic viscosurgical devices. B) Aspirating speculum.

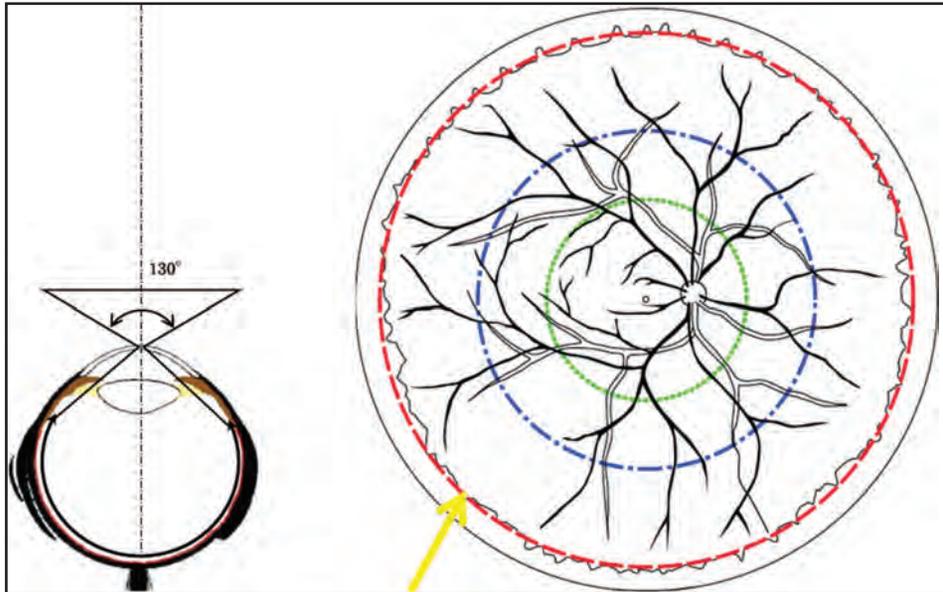


Figure 8: The field of view of OFFISS, 120-D lens.

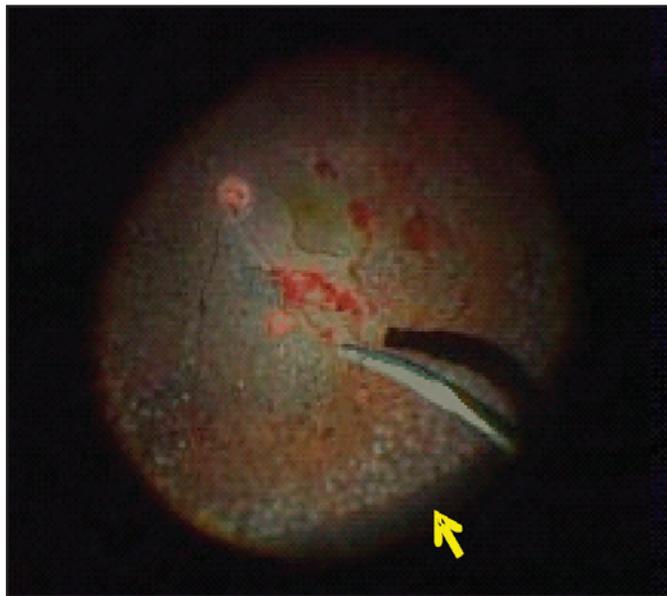


Figure 9: OFFISS, 120-D lens can observe ora serrata.



Table 2: Wide-Angle Viewing System Comparison Table

	Contact		Non-Contact	
	ClariVIT, MiniQuad, etc	BIOM	OFFISS	Peyman-Wessels -Landers
microscope	all	Zeiss, Leica, etc	Topcon (OMS -800)	all
inverter	SDL,ROLS, Inverter tube	SDI, ROLS, Inverter tube	automatic SDI	unnecessary
price	inexpensive	expensive	most expensive	relatively inexpensive
maximum field of view	over 130 degrees	120 degrees	over 130 degrees	100 degrees
bimanual vitrectomy	chandelier	chandelier	40-D lens, chandelier	chandelier
focus	electric (microscope)	manual (field lens)	electric (field lens)	manual (field lens)
alignment	electric (microscope)	electric (microscope)	electric (field lens)	electric (microscope)
easiness of focus and alignment	relatively difficult	relatively difficult	relatively easy	relatively difficult
observation field (fluid)				
phakia	vitreous base	equator~vitreous base	vitreous base	equator
pseudophakia	vitreous base~ora serrata	vitreous base	vitreous base~ora serrata	equator~vitreous base
aphakia	ora serrata~pars plana	vitreous base~ora serrata	ora serrata~pars plana	vitreous base
observation field (air)				
phakia	ora serrata	vitreous base	ora serrata	equator~vitreous base
pseudophakia	ora serrata~pars plana	vitreous base~ora serrata	pars plana	vitreous base
aphakia	pars plana~pars plicata	ora serrata~pars plana	pars plana~pars plicata	vitreous base~ora serrata

The disadvantage of the OFFISS system is the fact that it is mounted only one microscope (OMS-800), therefore it is most expensive for that.

The chandelier-style endoilluminator (Chandelier; Synergetics Inc, St Challes, Missouri, USA) produces homogeneous and wide-angle endoillumination, making it suitable for use in combination with this system for obtaining a glare-free and panoramic viewing (Figure 12).¹⁰ Because of its hands-free nature bimanual

manipulation is possible during removal of strongly adherent preretinal membranes in patients with diabetic retinopathy and proliferative vitreoretinopathy (Figure 10). However, this system is not suitable for delicate surgical procedures in the posterior pole. We have used magnifying quartz contact lens with HHV silicon holder (HOYA health care, Tokyo, Japan) for delicate procedures such as internal limiting membrane and epiretinal membrane peeling (Figure 11). With OFFISS, 120-D and wide-angle endoillumination, all requirements



Figure 10: Bimanual method by OFFISS, 120-D lens with chandelier.



Figure 11: Epiretinal membrane peeling by magnifying lens.

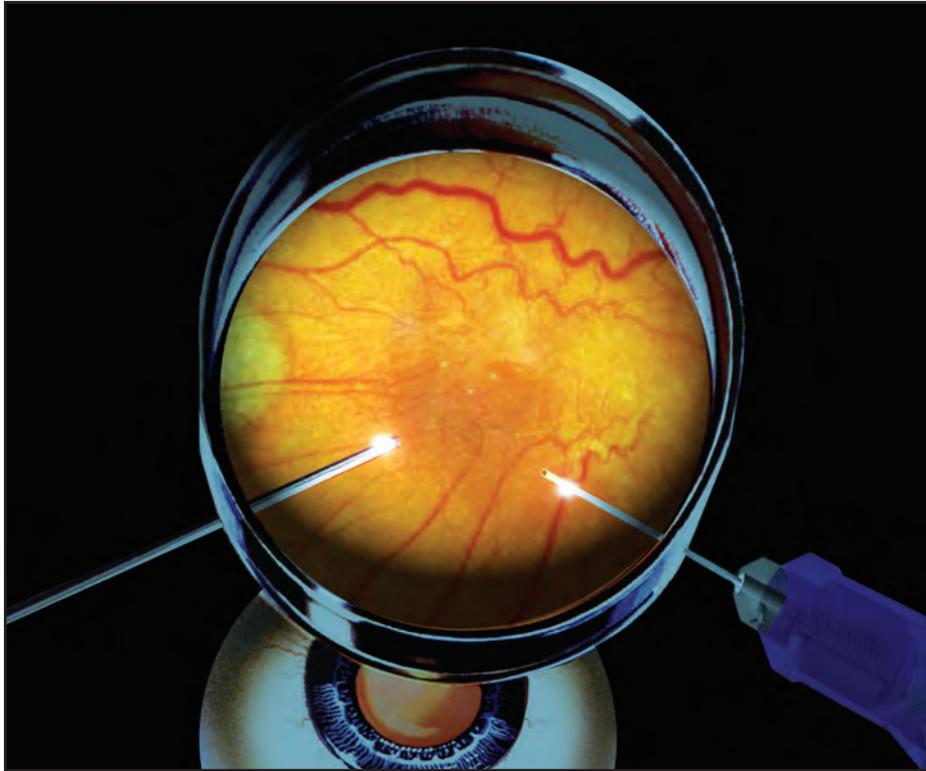


Figure 12: This visual technology provides a wide range of excellent visualization necessary during the pars plana approach. (Art from Jaypee-Highlights Medical Publishers).

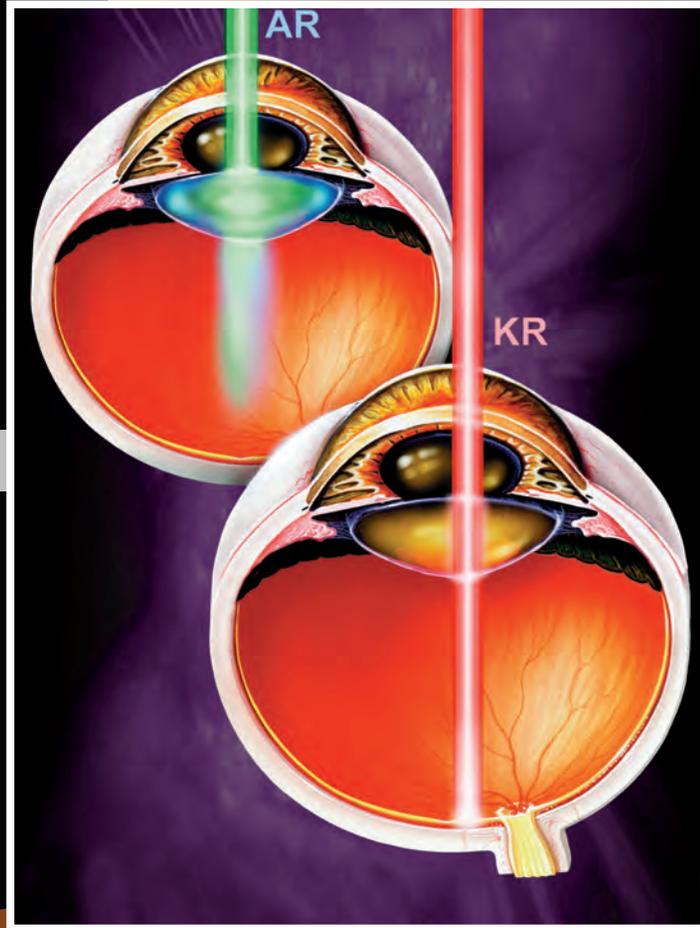
for wide-angle observation, panoramic viewing vitreoretinal surgery and constant bimanual vitreoretinal surgery are met. The surgeon does not need an assistant, operation time

is shortened, the risk of complications is minimized and complicated cases with severe vitreoretinal pathology are easier to handle.



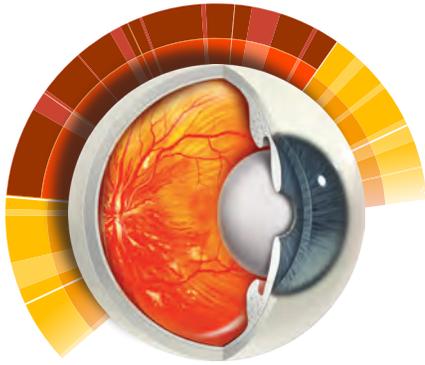
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Section 2

Laser Photocoagulation



6

Practical Aspects of Laser Photocoagulation

NELSON SABATES, MD,
SAVAK TEYMOORIAN, MD, MBA,
FELIX SABATES, MD

Fundamental Principles of Laser Energy

Laser Energy as Applied to Retinal Diseases

Laser photocoagulation is the transfer of light energy into heat energy that denatures proteins and produces tissue coagulation. Laser light can be more concentrated than normal light leading to more efficient heat production in the target tissue. The spectrum of laser wavelengths that will be discussed in this section as applied to laser treatment of the retina extends from blue light around 400 nm (Figures 1 - 2) to red light around 780 nm (Figures 5 - 7). Between those are pure green (Figure 3) and yellow light (Figure 4). The infrared wavelength of 800 nm used in the diode laser is longer than the visible 780 nm of red (Figures 8 - 9).

Wavelengths shorter than 400 nm are the ultraviolet, x-rays and gamma rays. Shorter wavelengths (blue) provide more energy per photon than the longer ones (red). Therefore, lasers with shorter wavelengths are more damaging to the retinal tissues.

Types of Lasers Used for Retinal Therapy

The output of a laser can be classified as continuous-wave or pulsed. Although these terms are used throughout ophthalmology, their significance may not be quite clear to those colleagues who do not use lasers often. For practical understanding, retinal photocoagulation is usually performed with a continuous-wave laser. In continuous-wave lasers, a pumping source constantly excites the lasering material and radiation is continuously emitted. The output for retinal photocoagulation is usually delivered



during an interval of 0.1 to 1.0 seconds. In contrast, pulsed laser operation occurs when a flash lamp or other pumping source turns on and off causing pulses of laser light to be generated. Pulses are usually less than 1 millisecond.

Evolution of Photocoagulation for Retinal Diseases

Photocoagulation of the retina has undergone rapid and steady development since the first Xenon arc instrument developed by Meyer-Schwickerath and produced com-

mercially by Zeiss in 1956. Laser technology has provided better and more reliable instrumentation (Figures 1-9). Photocoagulation has evolved from intense polychromatic white light sources like the xenon lamp, to gas lasers (argon blue-green and green, and krypton yellow and red), and most recently to solid-state diode lasers.

The first decade of laser photocoagulation of the retina was marked by steady refinement in the quality of the spectral delivery. This resulted in the elimination of the blue portion of the spectrum because it was more damaging to the retina (Figure 1). It also

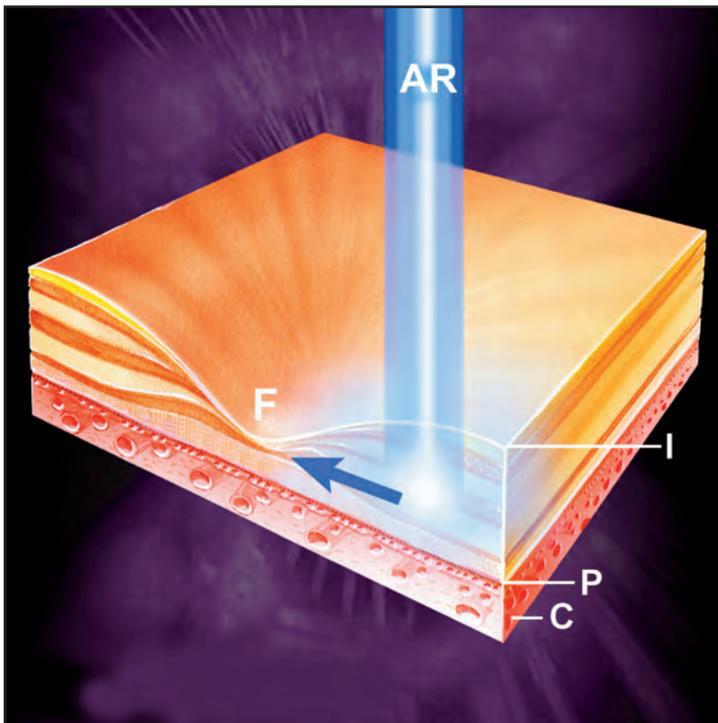


Figure 1: Disadvantages of Argon Blue Laser in Retinal Treatment. Retinal damage occurs with the blue light of the argon laser (AR) through scattering (arrow) within the retina. The blue light is also absorbed by the yellow pigment present in the inner layers of the macula (F) which produces damage to the retina during macular photocoagulation. Blue light is also absorbed at the pigment epithelium level (P) which is anterior to the choroid (C). (Art from Jaypee Highlights Medical Publishers).



made available specific wavelengths that maximize absorption while requiring less power (Figures 3 - 9). These modifications helped achieve the desired therapeutic results while simultaneously generating less damage to the surrounding normal retinal tissue. A pure green wavelength was attained by the addition of a green filter that only transmits the monochromatic green band that the argon laser emits.

Indications and Availability of Laser Equipment

Indications for laser therapy have been expanded through landmark multicenter studies that have proved to create beneficial effect on diabetic retinopathy and subretinal neovascular membranes in macular diseases. With the availability of less expensive and smaller instruments, laser technology is now widely available. This includes not only retinal centers in academic institutions that employ retina specialists but also many private offices throughout the world that are managed by highly trained general ophthalmologists. Although there are well known advantages for the different wavelengths, green has been the most popular due to its availability in low cost instrumentation and the wide range of its applications (Figures 3 - 6).

How to Improve Your Results

Importance of Power Density Delivery

It is important to understand the concept of power density when applying a coagulat-

ing beam to diseased tissue. The spot size, power setting and exposure time determine the power density of the laser. By convention, the spot size is selected prior to treatment while the power setting and exposure time are adjusted throughout the laser treatment. Protocols for controlling these variables have been established for different applications and indications.

Maintaining the correct power density requires careful attention to the relationship of spot size, exposure time and power. Once a good power density has been found, the power and exposure interval should be kept constant as long as the spot size does not change. Any decrease in spot size should be accompanied by a decrease of input power. However, in practice there are multiple factors that will affect the size of the spot and power density such as wavelength, media opacity, and the absorption quality of the tissue to be treated.

The ophthalmologist treating patients with laser photocoagulation should become familiar with a limited number of laser wavelength and contact lens combinations to develop expertise with the factors that will affect the correct power density delivered by the different lasers used. Several good quality contact lenses are available, each with its own advantages and disadvantages.

Pearls for Treatment in the Macular Area Close to the Fovea

Most procedures are performed under anesthetic drops although occasionally retrobulbar anesthesia is required. When treating close to the foveal area, special care needs to be

taken to avoid injury to this important area. Patient cooperation is critical. They should be made aware of any possible distraction that may occur during treatment. For example, the shutter noise of the instrument and anticipation of the laser application may produce a slight movement of the eye causing damage to the central foveal area.

Other considerations when treating near the fovea include the laser settings used. An example of possible settings begins with a 100 micron spot, a short exposure of 0.1 - 0.2 seconds, and a low power intensity of 100 milliwatts or less. The power can then be slowly increased until the desired reaction is obtained.

Selection of the appropriate wavelength is also important. For instance the use a red wavelength will allow for better penetration through early opacification of the lens (Figure 2). This decreases the need for greater power density.

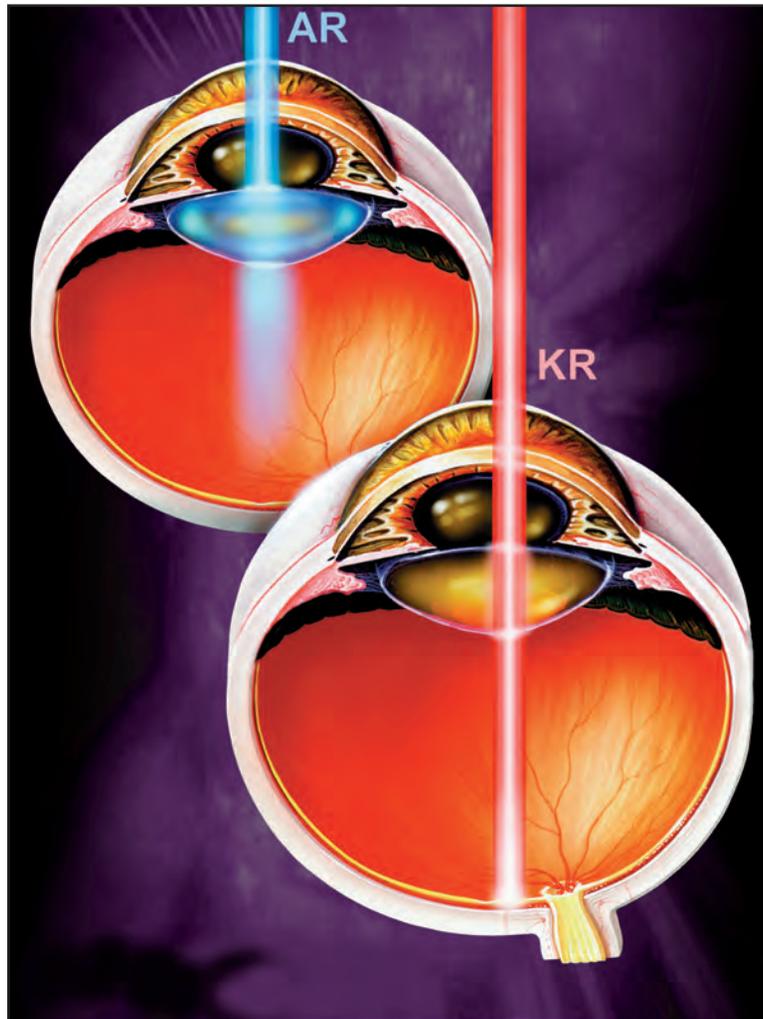


Figure 2: Disadvantages of Argon Blue Laser in Presence of Yellow Lens from Aging. The blue light of the argon laser (AR) is absorbed by the yellow lens of an aging eye with risk of damage at this level. (Below) The red light of the Krypton laser (KR) is absorbed less by a yellow lens and thus more energy reaches the retina with little effect on the lens. (Art from Jaypee Highlights Medical Publishers).



Monitoring and Titration During Extensive Photocoagulation

In cases where extensive photocoagulation is required, the ophthalmologist should constantly monitor the retinal reaction since this can vary markedly from one spot to the next depending on the amount of tissue absorption. Titration for the correct amount of energy is critical.

Pearls in the Treatment of Proliferative Diabetic Retinopathy

When an advanced stage of proliferative diabetic retinopathy is present, large numbers of laser application spots are usually necessary. It is recommended to deliver these in multiple stages to avoid exudative choroidal and retinal detachment not infrequently found after extensive treatment. In patients where neovascularization at the disc or elsewhere remains with recurrent bleeding in spite of adequate photocoagulation, further laser treatment should not be insisted. Vitrectomy with endolaser photocoagulation (Figure 9) should be applied without delay to avoid permanent damage.

Timing for Vitrectomy

In proliferative diabetic retinopathy, it is preferable to intervene early with vitrectomy when indicated rather than later. This avoids the production of a small visual field as a result of increased laser scarring following extensive photocoagulation. Ophthalmologists must remain flexible in their laser applica-

tion to the retina is important to obtain the desired results with the least application of energy possible. The goal is to spare retina rather than to destroy retina.

Comparative Tissue Effects of Different Lasers

The Blue Laser

The argon laser that incorporated blue and green wavelengths was used for many years in the treatment of chorioretinal diseases. The majority of commercial argon laser photocoagulators available during the 70's produced a light beam of 70% blue (488 nm) and 30% green (515 nm). Treatment with the blue wavelength has been discontinued for use in retinal photocoagulation in favor of many others, especially the green wavelength.

Disadvantages of the Blue Laser Light in the Treatment of the Retina

Photochemical (non-thermal) retinal damage is higher with lasers of shorter wavelengths (blue) than those having longer wavelengths (green, yellow, red and infrared). This is because shorter wavelengths create more energy per photons. Blue is scattered many times more in the media than the green, yellow or red. Therefore, higher energies are needed to obtain the desired absorption by the lesion to be treated. Scattering in the ocular media (Figure 2) increases with changes from aging so higher power levels



at the cornea are necessary to obtain the desired retinal burn. Also, it is possible that scattered blue light could damage normal retina next to the treatment area (Figure 1). These were some of the reasons why the blue part of the argon spectrum was eliminated for retinal treatment.

Blue light is absorbed by the yellow pigment present in the inner layers of the macula (Figure 1) producing damage to these vital tissues during macular photocoagulation. This may increase visual field defects from the treatment of macular lesions.

Also, the yellowed lens in aging eyes and cataract opacities increase absorption of blue light. This produces higher energy uptake by the crystalline lens with subsequent risk of damage (Figure 2).

The Green Laser

The green argon laser light has a wavelength of 515 nm. This laser is the most widely available and popular laser for retinal photocoagulation. It can be found in the following types of lasers: 1) lasers made exclusively for pure green output or 2) a blue-green laser with filter to provide the pure green wavelength.

Advantages of the Green Laser Compared With Red

The green wavelength has the advantage of being absorbed by the hemoglobin of the blood in a subretinal neovascular membrane (NM) (Figure 3). The disadvantage is when

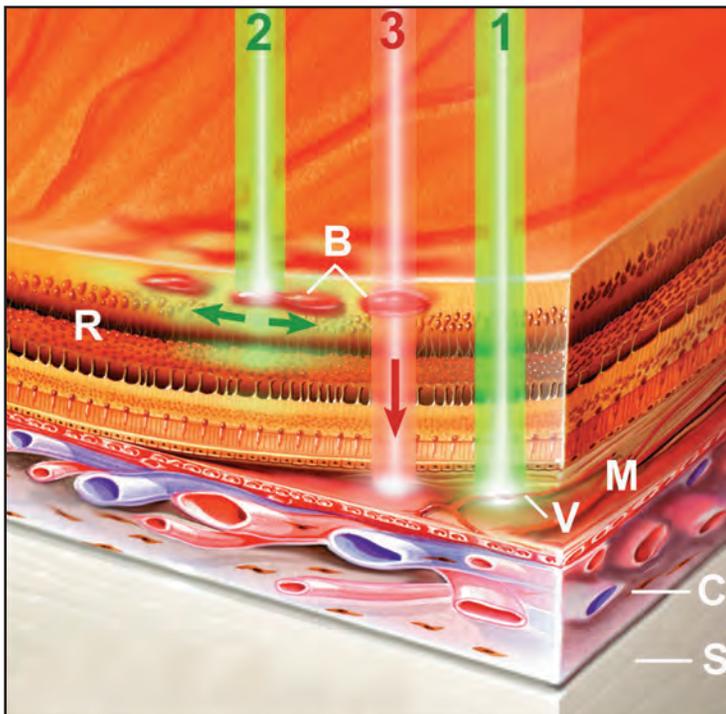


Figure 3: Advantages of Green Laser Wavelength - Disadvantages with Intra-retinal Blood. (1) The green wavelength has the advantage of being absorbed by the hemoglobin of the blood vessels of a subretinal neovascular membrane (M). (2) However, when a small layer of blood is present in the inner layers of the retina (intra-retinal blood), the green light will be absorbed by the hemoglobin thereby producing damage (green arrows) to the inner retinal layers. On the other hand, red light (3) will penetrate deeper (red arrow) due to the lack of absorption by hemoglobin. Choroid (C) and sclera (S). (Art from Jaypee Highlights Medical Publishers).

a small layer of blood (B) is present in the inner layers of the retina (intraretinal blood), the green light (G) will be absorbed by the hemoglobin. This absorption of energy will damage the inner retinal layers (Figure 3). Red light (R) will penetrate deeper due to the lack of absorption by hemoglobin.

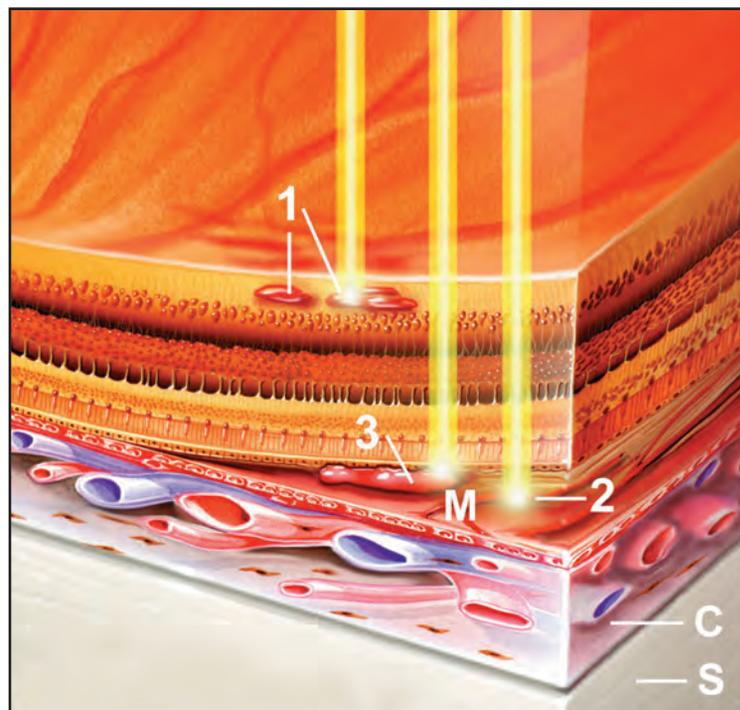
Advantages of the Yellow Laser Compared With Red

Yellow (Figure 4), as well as green, laser light is maximally absorbed by hemoglobin. This allows direct treatment of superficial retinal vascular lesions and subretinal neovascular membranes. The absorption of yellow

and green light by hemoglobin becomes a disadvantage when the subretinal neovascular membrane (NM) lies under a thin layer of subretinal hemorrhage (H). The yellow and green laser energy is first absorbed by the layered blood (H) before affecting the deeper structures. On the other hand, red laser light can penetrate these hemorrhages.

The yellow laser wavelength is not frequently used due to the cost of instrumentation and equipment. It still remains, however, the best wavelength to treat vascular lesions due to the increased absorption by oxyhemoglobin. This requires less power to obtain the tissue reaction needed to coagulate the vascularized tissue.

Figure 4: Advantages and Disadvantages of Green and Yellow Lasers. Yellow, along with green laser light, is maximally absorbed by hemoglobin. This allows direct treatment of superficial retinal vascular lesions (1) and subretinal neovascular membranes (2). This absorption of yellow and green light by hemoglobin becomes a disadvantage when the subretinal neovascular membrane (M) lies under a thin layer of subretinal hemorrhage (3). The yellow and green energy are first absorbed by the blood in layer (3) before having the desired effect in deeper structures. On the other hand, the red laser light can penetrate these hemorrhages. Other anatomy: Choroid (C) and sclera (S). (Art from Jaypee Highlights Medical Publishers).





The Red Krypton Laser

The red laser uses a wavelength around 647 nm. It continues to be used in some retinal diseases such as age-related macular degeneration (ARMD) (Figure 5), but it is not as popular now as the green wavelength.

Advantages of the Red Laser

The red laser is particularly effective when coagulating tissue or subretinal neovascular vessels that lies under a thin layer of subretinal hemorrhage (Figure 6). Red light produces less scatter irradiation and heat into the retina from the blood. This preserves the desired retinal tissue, in particular when treating near the fovea (Figure 7).

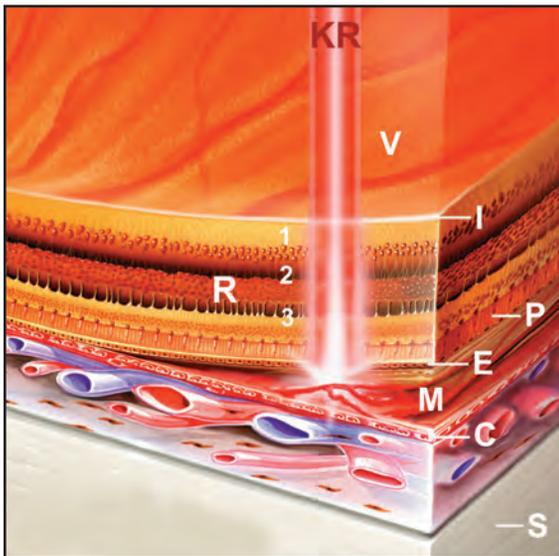


Figure 5: Advantages of Red Krypton Laser with Subretinal Neovascular Membrane in ARMD. Above is shown a cross section of the retina and choroid emphasizing the area of a subretinal neovascular membrane (M) that lies between the pigment epithelium layer (E) and choriocapillaris (C). This area of fibrous growth is vascularized by outgrowths from the choroid and is a very important complication of exudative ARMD. Note that the retina (R) is detached in this area. The red Krypton light (Kr) travels through the vitreous (V) with very little involvement of the nerve fiber layer seen at area 1. There is less absorption of laser light within the inner retina at area 2. Lack of absorption in the inner layer results in decreased intraretinal fibrosis at area 3. Here the surgeon aims at occlusion of choroidal blood vessels that is the possible source of the subretinal neovascular membrane (M). Other anatomy: Photoreceptors (P) and sclera (S). (Art from Jaypee

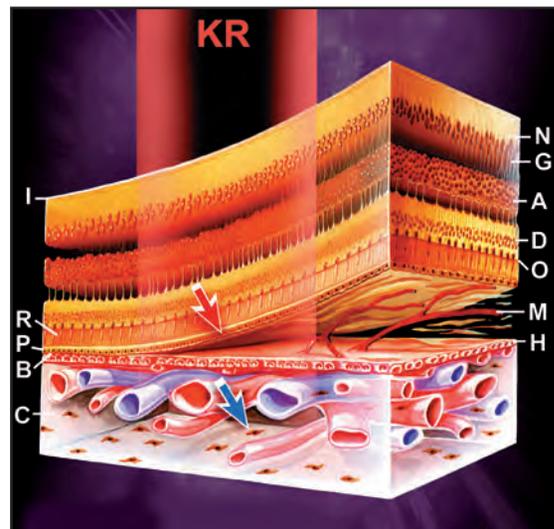
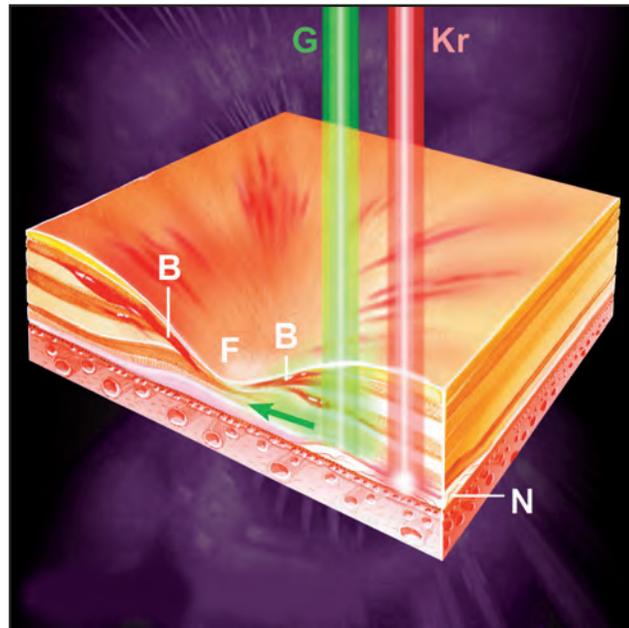


Figure 6: Location of Krypton Red Laser Absorption in Treatment of Subretinal Vascular Membrane. This anatomical cross section of the retina shows that red laser light (KR) is mainly absorbed by the melanin (blue arrow) of choroid (C) and retinal pigment epithelium (P-red arrow). The retina is shown detached in the area of the subretinal vascular membrane (M). Other retinal anatomy: inner limiting membrane (I), ganglion layer (G), inner nuclear layer (A), outer nuclear layer (D), outer limiting membrane (O), rod and cone layer (R), Bruch's membrane (B) and choriocapillaris (H). (Art from Jaypee Highlights Medical Publishers).



Figure 7: Red Laser Light with Intraretinal Blood Near Fovea. Red light (Kr) is the method of choice when treating subretinal neovascular membranes (N) near the fovea (F) when blood (B) is in the center of the fovea, where it is commonly found. One gets less scatter irradiation and heat into the fovea via the blood such as found with the green laser (green arrow), thus avoiding the destruction of the fovea. (Art from Jaypee Highlights Medical Publishers).



There are also other advantages of the red krypton laser. It provides deeper tissue penetration leading to coagulation of the subretinal neovascularization or subretinal neovascular membrane (Figure 5). There is less energy absorption by the inner retina (Figures 6 - 7). This leads to less involvement of the nerve fiber layer and decreased intraretinal fibrosis. There is less absorption of the laser light by the macular yellow pigment or blood in the macula. This is critical as it limits the damage to the fovea and thus minimizes the decrease in visual acuity immediately following treatment.

Disadvantages of the Red Laser

The main disadvantage of red krypton laser is that its use may lead to choroidal bleeding. The best way to avoid this complication is to abstain from using short exposures with a small spot and high intensity.

The Pure Monochromatic Green Laser Compared to Red Krypton

If red krypton equipment is available as shown in Figure 7, it is better to use red in cases with intraretinal blood. In all other instances as shown in Figures 5 and 6, a pure green wavelength is as good as red krypton. For treatment of subretinal neovascular membranes, a key complication of ARMD, the red wavelength has not been demonstrated to be better than pure green unless there is intraretinal blood, as shown in Figure 7.

If dealing with superficial retinal neovascularization such as in diabetes and vascular tumors, the krypton red laser is not indicated because it is not absorbed by hemoglobin. Those cases are better treated with green or yellow wavelengths.



The Diode Laser

The diode laser produces an infrared light with long wavelengths in the range of 700-820 nm. The efficiency of semiconductor diode lasers makes it possible for them to have minimal electrical or cooling needs. They can be made small, portable and even be mounted on existing slit lamps. Their solid-state design allows them to be made economically and reliably.

Main Uses for Diode Laser

This laser is used for direct retinal photocoagulation either transclerally for treating retinal pathology such as retinal tears or holes, diabetic macular edema, and proliferative diabetic retinopathy; or for use in endophotocoagulation. It can be utilized in photodynamic therapy for subretinal neovascular membranes in ARMD (Figure 8). The diode laser can also be used effectively in non-retinal diseases particularly for cyclodestructive procedures in glaucoma.

Advantages of the Diode Laser

In the presently available commercial lasers, the diode laser has several advantages. Because of decreased scatter and absorption, the infrared diode laser penetrates vitreous hemorrhage and nuclear sclerotic cataracts better than the shorter wavelength laser such as green and yellow. The deeper penetration spares the inner sensory retina. The laser can be delivered through diabetic preretinal membranes without contracting them. The

absence of xanthophyll absorption along with the lower absorption for melanin and oxyhemoglobin provides safe delivery to the macula (Figure 7). The lack of hemoglobin absorption allows penetration through thin layers of preretinal or subretinal hemorrhage without excessive laser energy uptake (Figure 8).

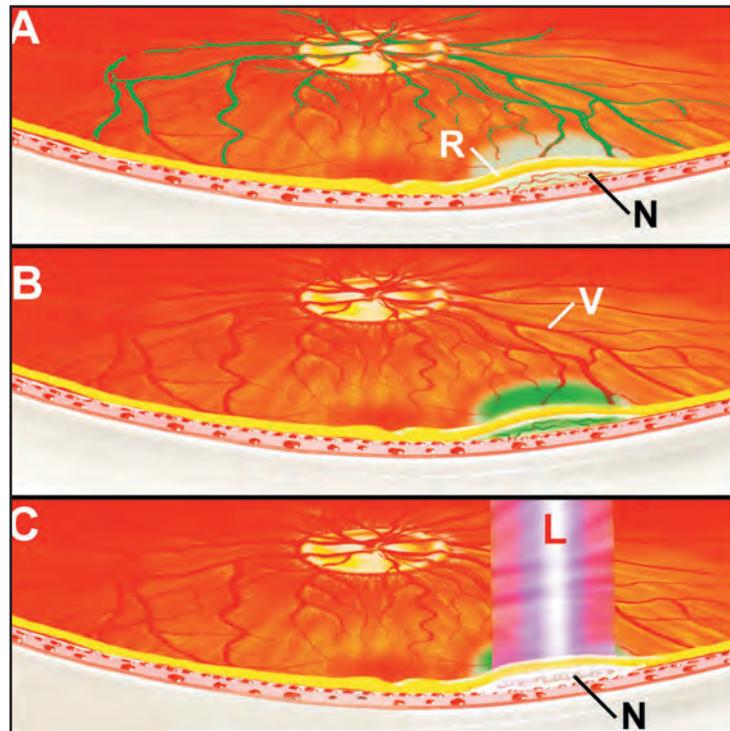
Other Advantages of the Diode Laser

Its portability has been very useful given the many locations where laser treatment can be delivered. This is particularly important in the operating rooms of many hospitals throughout the world. Despite the inevitable trauma to the equipment that comes from moving it, there is no damage to the function of the laser. Without the need for cooling or triphase 220-volt power, laser therapy can be performed in any room containing a Haag-Streit slit lamp or endophotocoagulation system. The diode laser can be connected to an AC source of electrical power or can be powered by batteries if needed. The solid-state design of the laser makes it resistant to extremes of humidity and temperature.

Disadvantages of the Diode Laser

Vascular abnormalities such as retinal angiomas or retinal telangiectasia cannot be directly treated with the 800 nm wavelength because it is not absorbed by hemoglobin. Its use may be inadequate in subretinal neovascular membranes in light-colored fundi because of low laser light absorption. Broad-field

Figure 8: Uses of the Diode Laser. The diode laser is a solid-state, infrared laser of long wavelength 700-820 nanometers in the present commercial models. It represents the most recent technology that is the solid-state laser. It can be made small and portable. The laser is well transmitted by the ocular media, and absorption by melanin and oxyhemoglobin is lower. The diode laser may be used in direct retinal photocoagulation either through the traditional slit lamp system or through endophotocoagulation, transcleral irradiation for retinal pathology such as retinal holes, and cyclodestructive procedures in glaucoma (not shown). (Art from Jaypee Highlights Medical Publishers).



contact lenses are suitable for photocoagulation with the diode laser. These produce inverted and real images. Lenses that work well with the diode laser include the Volk Centralis, Trans-Equator, and Quadraspheric; and the Mainster Standard and Widefield.

SYSTEMS TO DELIVER LASER ENERGY

After the clinician has decided which wavelength to use, the next question is which system to use to deliver the laser energy. Delivery systems include the traditional slit-lamp system, endofiberoptics for use intraocularly such as in endolaser photocoagulation, the indirect ophthalmoscope,

and contact probes. All ophthalmologists are familiar with the slit-lamp delivery system which is the most commonly used. Consequently, single spot treatment will not be discussed here except for the relatively new PASCAL treatment. The rest of the focus will be about the endolaser and binocular indirect ophthalmoscopic delivery system.

PASCAL Photocoagulation

PASCAL Coagulation Background

The PASCAL (Pattern Scan Laser) coagulation system by OptiMedica is a recent development intended to expand upon the current single laser spot used in coagulation



therapy. This modified slit lamp coagulator uses a 532 nm laser that provides multiple spot therapy of up to 56 in number that are applied in pre-arranged configurations such as squares and arc arrays. These arrays can be adjusted to provide faster and more efficient laser applications depending upon the desired treatment.

Indications for PASCAL Photocoagulation

The PASCAL coagulation therapy has indications for both posterior and anterior segment ocular pathology. Retinal uses include panretinal, focal, or macular grid treatment in patients with proliferative diabetic retinopathy, retinal tears and detachments, choroidal neovascularization, age-related macular degeneration, and branch retinal vein occlusions. The anterior segment uses include trabeculectomy and iridectomy, but further discussion about these applications is beyond the scope of this chapter.

Advantages of PASCAL Coagulation

This treatment method provides efficient laser therapy over large areas of the retina using multiple spots in a rapid successive order. The pattern and number of spots can be adjusted depending on the desired location. It is also versatile in its uses from large panretinal therapy requiring hundreds of spots to localized single spot focal treatment. This rapid therapy is believed to provide less patient discomfort by shorting

both laser time between each spot application and total time at the slit lamp.

Disadvantages of PASCAL Coagulation

There are some disadvantages to this coagulation treatment. Patients need to be able to sit at the slit lamp for the therapy. Once situated, their cooperation is critical as multiple spots are delivered in successive order after activation. Sudden movements by patients can result in coagulation of unintended locations.

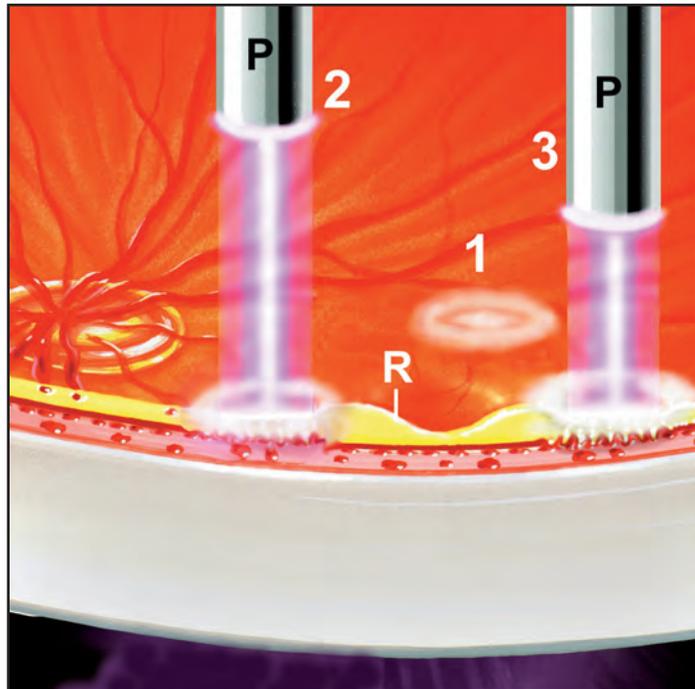
Endolaser Photocoagulation

Endolaser Coagulation Background

Endolaser coagulation is a method by which the laser light is brought directly inside the eye through a fiberoptic to apply treatment to the retina (Figure 9). This is in contrast to conventional laser photocoagulation that is performed through the clear cornea also known as the “transpupillary” method. The endolaser is essentially used only during vitrectomy. When the surgeon is working inside the eye and a need for coagulation exists, the laser light is directed directly toward that area through a 1 mm diameter probe and photocoagulation is performed. Also, if a hemorrhage occurs during surgery, the media can turn too cloudy for transpupillary application. Since the surgeon cannot bring the patient to the slit lamp, photocoagulation can be completed with the endolaser (Figure 9).



Figure 9: Endolaser Does Not Touch the Surface of Retina. The proper wattage to use for endophotocoagulation should result in a faint whitish reaction on the retina (1). These threshold lesions should be obtained with the tip of the laser probe (P) about 2 disc diameters from the retinal surface as shown at (2). (3) A stronger laser reaction on the retina can be accomplished by increasing exposure time or bringing the probe (P) slightly closer to the retina (R). The instrument never touches the surface of the retina, saving adjacent structures from damage. (Art from Jaypee Highlights Medical Publishers).



Indications for Endolaser Photocoagulation

What is now done now with an endolaser was previously performed through intraocular diathermy, external cryocoagulation, or endocryotherapy. These methods have been almost abandoned and replaced by the endolaser.

The indications for the use of endolaser during vitrectomy are: 1) to coagulate pre-existing, posteriorly located retinal tears or iatrogenically produced retinal tears; 2) to assist with the internal drainage of subretinal fluid in retinal detachment; 3) to coagulate bleeding retinal surface neovascularization;

4) to perform panretinal photocoagulation in diabetic patients immediately after vitrectomy; and 5) to manage penetrating injuries and intraocular foreign bodies.

Comparison with Other Methods Previously Used

When using an intraocular diathermy probe, the probe needs to be close to the retina nearly touching the tissue. During coagulation the tissue can adhere to the probe resulting in the instrument itself inflicting damage to the retina and choroid. The surgeon can actually create a choroidal hemorrhage by accidentally penetrating the choroid and not coagulating it.



When intraocular cryotherapy is used, the probe has to be held motionless inside the eye on the retina. The effect of coagulation starts on the retinal side and then penetrates deeper into the choroid. This produces a larger reaction in the sensory retina than in the pigment epithelium and choroid. If the probe is not held still, the retina can be fractured at the edge of the cryocoagulation and could create a new tear.

The disadvantage of external cryotherapy versus endolaser in treating posteriorly located retinal tears is that a large area of the retina has to be coagulated that may lead to damage in the nearby fovea and optic nerve. In addition, the sealing of tears close to the fovea or to the optic nerve is a more complex procedure technically when external cryotherapy is used because of their location.

Binocular Indirect Ophthalmoscopic Laser Photocoagulation (BIOLP)

BIOLP is an essential tool for those who want to treat peripheral retinal neovascularization. The advent of this laser delivery system allows the surgeon to visualize and treat the retinal periphery easily, an important advancement. Laser treatment delivered by means of BIOLP has made possible the treatment of peripheral retinal neovascularization.

Indications and Advantages of the BIOLP

The BIOLP has several indications. It can be used for panretinal photocoagulation in

patients with proliferative diabetic retinopathy who cannot sit at a slit lamp. Other indications include treatment for peripheral retinal tears and demarcation of localized retinal detachments. BIOLOP can also be used in retinal vascular diseases affecting the periphery as in some cases of branch retinal vein occlusions, central retinal vein occlusions, retinopathy of prematurity, and for inflammatory and retinal diseases. This technique also permits treatment of infants under general anesthesia and children without anesthesia if they are cooperative.

Since most of these diseases were treated in the past with cryopexy, it is important to point out that laser burns appear to produce faster adhesions and less breakdown of the blood-retina barrier. BIOLP is also of great value intraoperatively because it allows a wide view that is helpful for applying treatment to the peripheral retina.

Disadvantages of the BIOLP

In traditional slit-lamp delivery systems, the operator controls the spot size, power and duration. Spot size is difficult to control with the BIOLP. This requires special training to use it adequately and safely.

Duration and power are controlled in a manner similar to that for slit-lamp delivery systems and are titrated to achieve the desired burn. Care should be taken as the treatment moves farther to the periphery because the retinal spot may become smaller. Either the laser spot needs to be further defocused or the power decreased. It is best to deliver less power over a longer duration because the lesion produced can be better monitored.



Finally, it is difficult to treat within the macula, especially when first using the instrument. This is because small movements will shift the placement of the lesion and that spot size is difficult to determine precisely. The BIOLP is therefore best suited for patients with peripheral disease.

The duration and power needed depends on multiple factors including the wavelength of the laser, the clarity of the media, and the pigmentation of the retinal pigment epithelium. It is best to use at least 200 msec burns, because slower burns can be observed as they occur and breaks in Bruch's membrane may be prevented by stopping the treatment if the burns are becoming too intense. Lower power is needed with the argon BIOLP than with the infrared diode BIOLP if the media are clear. Conversely, in the presence of media opacity, the infrared diode BIOLP may need lower power than the argon BIOLP. Another note is that pigmented races need lower power and duration to achieve a white burn because the retinal pigment epithelium is more absorbent.

Availability of BIOLP Equipment

The latest versions are available as attachments to the argon laser, argon-krypton laser, frequency-doubled YAG laser, and infrared diode laser.

Anesthesia With BIOLP

Retinal burns with this instrument can be painful. Subconjunctival anesthesia should be used. Retrobulbar anesthesia is highly useful

to relieve pain but it has disadvantages. The patient cannot move the eye to the side of the lesion to facilitate visualization and treatment. When this happens, a cotton swab or other depressor can be used to move the eye or push the peripheral retina into view.

Adjusting the Aiming Beam

Once the eye is moved in the direction of the area requiring treatment, the aiming beam is adjusted so that it is in the middle of the retinal image. Power and duration are then titrated to achieve the burn required. If using a green wavelength, duration is set to 0.2 to 0.5 sec and power is increased as necessary. With the infrared diode laser, duration begins at 0.4 sec and power at 200 mW in a patient with well-pigmented retinal pigment epithelium. These change to 0.5 sec and 300 mW, respectively, in a patient with hypopigmented retinal pigment epithelium. The BIOLP delivery system has a greater potential of causing breaks in Bruch's membrane than does the slit lamp because keeping a consistent burn size is difficult.

Precautions Using the BIOLP

Other people in the treatment room should wear safety goggles. Windows should be covered to avoid exposing people outside the room to stray laser light, and a sign mandating the use of safety goggles should be placed on the door.

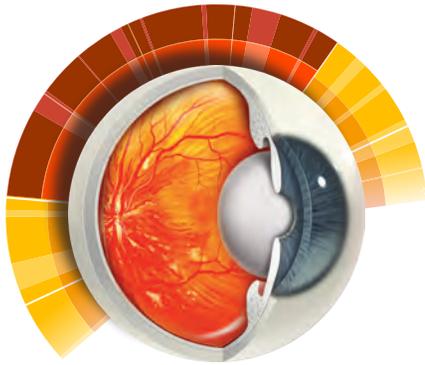
Because the eyelashes may absorb the laser energy and burn, a lid speculum can be used to hold the eyelids open since there



is no contact lens to do so. The cornea should be kept well lubricated because if it dries the epithelium becomes opaque.

Reference

PASCAL. Available at: <http://www.optimedica.com/default.aspx>. Accessed May 19, 2008.



Subthreshold Retinal Photocoagulation for Diabetic Retinopathy

JEFFREY K. LUTTRULL, MD

Diabetic retinopathy is the most common form of retinal vascular disease, constituting the main cause of visual acuity loss in patients with less than 50 years of age in developed countries, and increasing in prevalence daily.⁽¹⁻⁴⁾ The following discussion will focus on the most common visually threatening complications of diabetic retinopathy, especially diabetic macular edema (DME), as the paradigm for retinal vascular disease, and subthreshold retinal photocoagulation (SRP) as a method of treatment.

Conventional Suprathreshold Retinal Photocoagulation

The efficacy of retinal photocoagulation for the complications of diabetic retinopathy was established by the Diabetic Retinopathy Study (DRS, 1976), focusing on the treat-

ment of proliferative diabetic retinopathy (PDR); and the Early Treatment of Diabetic Retinopathy Study (ETDRS, 1985), focusing on the treatment of diabetic macular edema (DME) and the prevention of proliferative retinopathy. Despite major advances in the surgical and pharmacologic management of diabetic retinopathy in the decades since publication of these landmark studies, laser photocoagulation of the retina remains the mainstay of treatment, remarkably little changed in performance and conception. This chapter will examine how subthreshold retinal photocoagulation is effecting change in how photocoagulation for retinal vascular disease is performed, and understood, to the benefit of patients.

In the DRS and ETDRS, retinal photocoagulation was applied in a suprathreshold



fashion, using xenon arc (DRS) or argon laser (DRS and ETDRS) to produce grey to white retinal burns, leading to necrosis, inflammation, and finally fibrosis and atrophy (chorioretinal scarring) of the treated retina (Figure 1)⁽⁵⁾. The thermal retinal destruction inherent to conventional threshold and suprathereshold laser photocoagulation is the single source of the many well-known adverse effects that may cause immediate or late postoperative visual loss. These inherent adverse effects place

significant limitations on treatment density, intensity, location, frequency, repeatability and thus utility and effectiveness. Due to the effectiveness of conventional suprathereshold photocoagulation these inherent adverse treatment effects have been considered necessary evils. The results of SRP suggest however, that the complications and inherent adverse effects of thermal retinal destruction, while evil, are in fact not necessary.

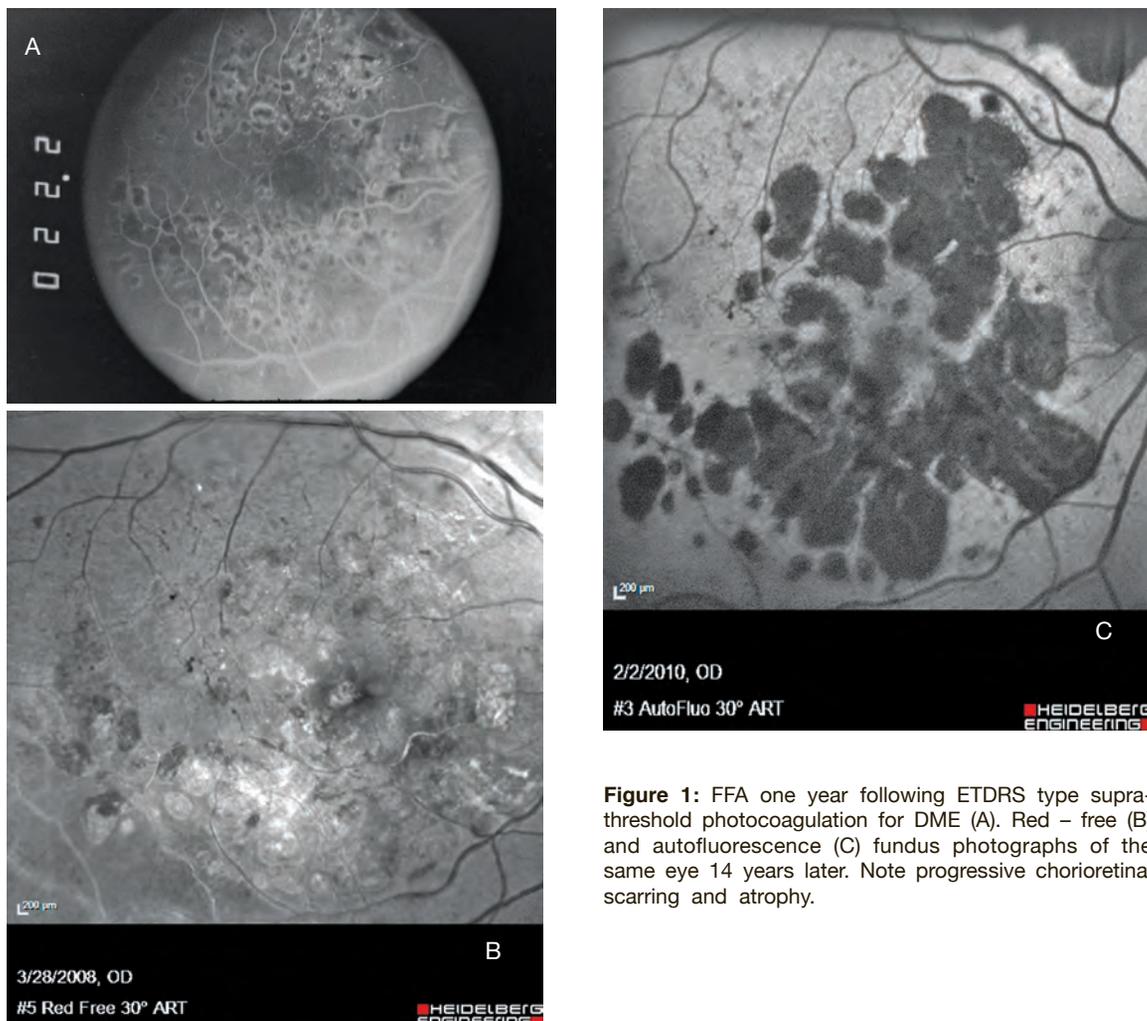


Figure 1: FFA one year following ETDRS type suprathereshold photocoagulation for DME (A). Red-free (B) and autofluorescence (C) fundus photographs of the same eye 14 years later. Note progressive chorioretinal scarring and atrophy.



In the DRS and ETDRS, observations were made which set the stage for subthreshold retinal photocoagulation. In the DRS, complications of treatment were found higher with increasing treatment intensity; treatment efficacy was found to increase with higher treatment density; and the most common and practically achievable result of treatment for PDR was arrest and regression rather than complete disappearance of new vessels.⁽⁶⁻⁹⁾ In the ETDRS, treatment risks and complications were also found to be higher with increasing treatment intensity, as well as proximity to the fovea; angiographic leakage was found to be a variable correlate rather than *sine qua non* of macular edema, with the risk of visual loss correlating more strongly with the location and extent of macular thickening than angiographic leakage (“clinically significant” DME, or CSME); that diffuse rather than focal angiographic leakage was associated with greater risk of disease progression and visual loss; and that angiographic leakage often persisted despite clinically effective treatment.^(5,8,10,11) The relevance of each of these observations to use of subthreshold retinal photocoagulation in the management of diabetic retinopathy will be discussed.

Subthreshold Retinal Photocoagulation (SRP) Defined

Traditionally, SRP is defined as retinal laser photocoagulation performed in such a way to produce a minimally visible, or acutely invisible treatment application endpoint.⁽¹²⁻¹⁴⁾ Typically, avoidance of an acutely visible threshold

(partial thickness) or suprathreshold (full-thickness) retinal laser burn is accomplished by reducing retinal laser power density, or irradiance (power applied per unit of retinal surface area), and consequently thermal rise. By reducing the tissue temperature rise it is hoped that the many well-known sight-threatening complications and unavoidable side effects of conventional visible end-point retinal photocoagulation might be minimized or prevented while still achieving effective retinal photocoagulation.

A cause and effect relationship between creation of a visible retinal burn and treatment benefit has been generally presumed.⁽¹⁶⁾ All traditional theories proposed to explain the effectiveness of laser photocoagulation for retinal vascular disease invoke creation of a chorioretinal scar as both fundamental and necessary. Remarkably, however, although the definite cause of all adverse treatment effects, chorioretinal scarring from thermal retinal destruction has never actually been proven necessary to produce the laser treatment benefits.

In the following discussion I coin a new taxonomy of SRP. This categorization will reflect the historical evolution of SRP from its roots in conventional suprathreshold photocoagulation, as well as critical practical, technical and clinical distinctions between different approaches often obscured by the single heading of “SRP”. In this new taxonomy I divide SRP into three categories, which I call “Classical”, “Clinical”, and “True” subthreshold retinal photocoagulation.



“Classical” Subthreshold Retinal Photocoagulation

In the ETDRS treatment of CSME was performed using suprathreshold photocoagulation directed at leaking macular microaneurysms, and/or placed in a grid pattern in areas of diffuse angiographic leakage associated with macular thickening. Confluent laser applications, and treatment near the fovea were avoided due to the risk of immediate treatment –associated visual loss. Direct thermal closure of angiographically leaking microaneurysms typically requires higher laser irradiances, increasing thermal retinal damage and scarring. Subsequently, it was learned that CSME could be effectively treated by grid photocoagulation alone, without direct treatment of microaneurysms. This led to movement away from low-density, high-intensity focal treatment to lower intensity grid treatment and the first attempts at SRP, which I term “classical” SRP.⁽¹⁷⁾

In classical SRP, the same continuous – wave (CW) laser used for suprathreshold retinal photocoagulation, argon green at first, later krypton red and diode infra-red lasers, was applied with reduced irradiance in a grid pattern (retinal burns separated by untreated intervals to avoid confluent retinal ablation) to the areas of macular thickening visible by contact lens biomicroscopy constituting CSME. The acute treatment endpoint sought is typically a barely visible burn, actually “threshold” rather than subthreshold, at the level of the outer retina and/or retinal pigment epithelium (RPE).⁽¹⁸⁾ Morphologic inconsistency is defining

characteristic of “classical” SRP. With classical SRP, retinal laser lesions tend to vary widely within the treatment field from invisible to suprathreshold, with many more lesions apparent by postoperative fundus fluorescein angiography (FFA) than by biomicroscopy. (Figure 2) The reasons for this variability of burn intensity with classical SRP will be discussed below under “A model for understanding...”. Thus, while effective, “classical” SRP may reduce, but not eliminate, the risks of conventional suprathreshold retinal photocoagulation.

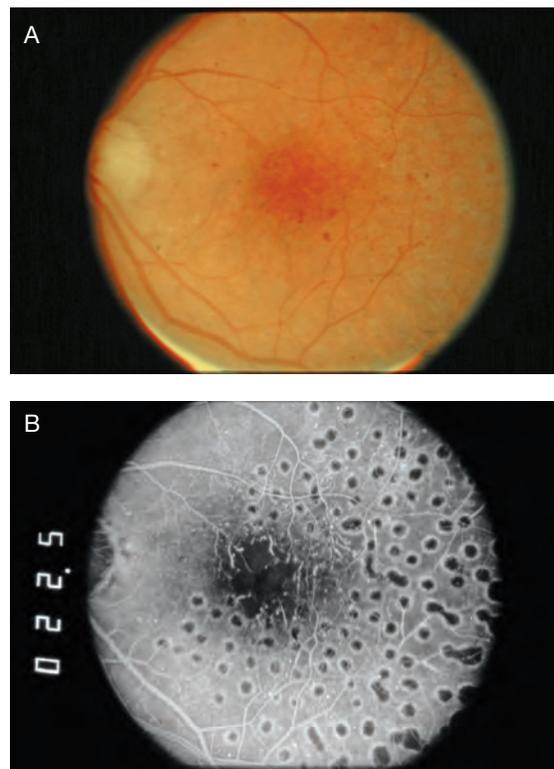


Figure 2: Macular appearance following “classical” subthreshold macular photocoagulation for diabetic macular edema. Note the subtle pigmentary disturbance seen clinically (A) and the obvious chorioretinal scarring demonstrated by FFA (B).

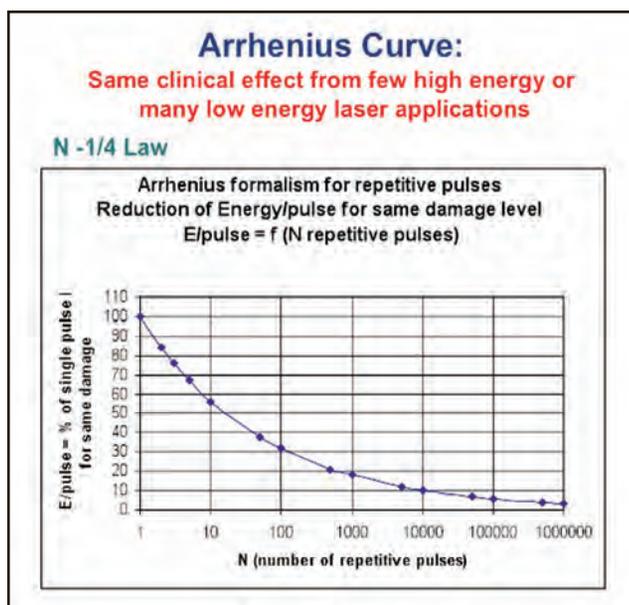


“Clinical” Subthreshold Retinal Photocoagulation

Introduced in the early 1990's the “micropulsed” (MP) laser emission modality enhanced the ability to perform SRP.⁽¹⁹⁻²³⁾ Employing an infra-red 810nm solid-state diode laser to maximize absorption by melanin in the RPE and choroid and minimize absorption by neurosensory retina, laser energy could be fired in short microsecond bursts (micropulses) separated by irradiance-free millisecond intervals. Shortening of the pulse duration enhanced localization of laser effects to the target RPE. The “duty-cycle” (DC), or the ratio of the laser bursts over the repetition period within a pulse train (exposure envelope), could be adjusted from a very low ratio, such as 5% (5%, or 100us “laser on” followed by 95%, or 1900us “laser off”) to a very high ratio, such as 95% (1900us “laser on”, 100us “laser off”). As the DC

increases the MP laser effects approach the clinical characteristics of a conventional CW laser due to tissue heating. If the “off” interval of the micropulsed laser exceeds the thermal relaxation time of the absorbing chromophore (in this case, the RPE melanin), photocoagulation effects could theoretically be achieved without producing clinically significant tissue heating, thus precluding laser-induced thermal retinal damage.^(14,15) Because of the much wider therapeutic window inherent in micropulsed vs. continuous wave photocoagulation (see below under “**A model for understanding...**”), SRP could be performed more reliably. The N^{-1/4} law, described by the Arrhenius curve, holds that the identical biologic effect can be produced by few high-energy laser applications or many low-energy laser applications. Thus, clinically subthermal subthreshold micropulsed retinal photocoagulation need not preclude clinically effective treatment (Figure 3).

Figure 3: The N-1/4 law illustrated by the Arrhenius curve demonstrating that the same biologic effect can be produced by few high energy, or many low energy laser applications.





Lead by Friberg, a number of investigators demonstrated both the effectiveness of clinical SRP for diabetic macular edema, and the predicted reduction in collateral thermal retinal injury over “classical” SRP.^(19,24–30) However, despite employment of micropulse technology, these reports also continued to describe persistent limitations in both safety and effectiveness. These limitations define “clinical” SRP. While clinically effective, these investigators continued to employ conventional grid laser application techniques, limiting the density of treatment and, therefore, potential treatment benefit. With regard to safety, all also continued to report a significant incidence of thermal retinal burns. However, unlike the retinal burns resulting from “classical” SRP, the lesions noted following “clinical” SRP were more likely acutely invisible, becoming increasingly apparent weeks and months following treatment, particularly by FFA.⁽³¹⁾

“True” Subthreshold Retinal Photocoagulation

In an attempt to realize the full potential of MP SRP a new treatment paradigm was reported, novel in that, for the first time, complete avoidance of any thermal retinal injury was chosen as a treatment goal coequal with achievement of clinically effective retinal photocoagulation.^(32–34) Successful implementation of these goals defines “true” SRP.

Focusing on the treatment of DME, performance of true SRP in the treatment of DME was achieved by two fundamental changes in treatment conception: First, to reliably avoid creation of any inadvertent thermal retinal burns, a small retinal laser spot size (125 μm),

to maximize heat dissipation was combined with very low micropulse duty cycle (5%), to minimize heat generation.

Practical elimination of the risk of thermal retinal injury by such “low intensity” micropulsed laser parameters allowed the second key change in treatment technique. Rather than applying low intensity photocoagulation focally or in a traditional low density grid of widely spaced applications, all areas of macular thickening due to DME up to the edge of the foveal avascular zone were treated confluent with contiguous laser applications, 360 degrees if indicated, even repeatedly with a single treatment session, to assure complete treatment coverage. The high density of laser application as well as potential proximity to the foveal center demanded absolutely consistent and reliable avoidance of any thermal retinal injury via “low – intensity” SRP. Thus, “true” SRP rests on these two necessary and complementary pillars of “high density” and “low intensity” micropulsed diode laser application.

Utilizing low intensity / high density micropulsed photocoagulation to perform true SRP (termed “SDM”, for “Subthreshold Diode Micropulse photocoagulation” by the authors), clinically effective treatment of DME and PDR were reported in pilot studies without any adverse treatment effects, or thermal retinal burns detectable by clinical biomicroscopy, FFA, or time-domain OCT.^(32–34) Subsequent observations demonstrate the absence of any laser-induced retinal injury with SDM by indocyanine green fundus angiography, fundus auto fluorescence photography, and Fourier-domain OCT with postoperative follow up of as long as 10 years⁽³⁵⁾ (Figures 4-6).

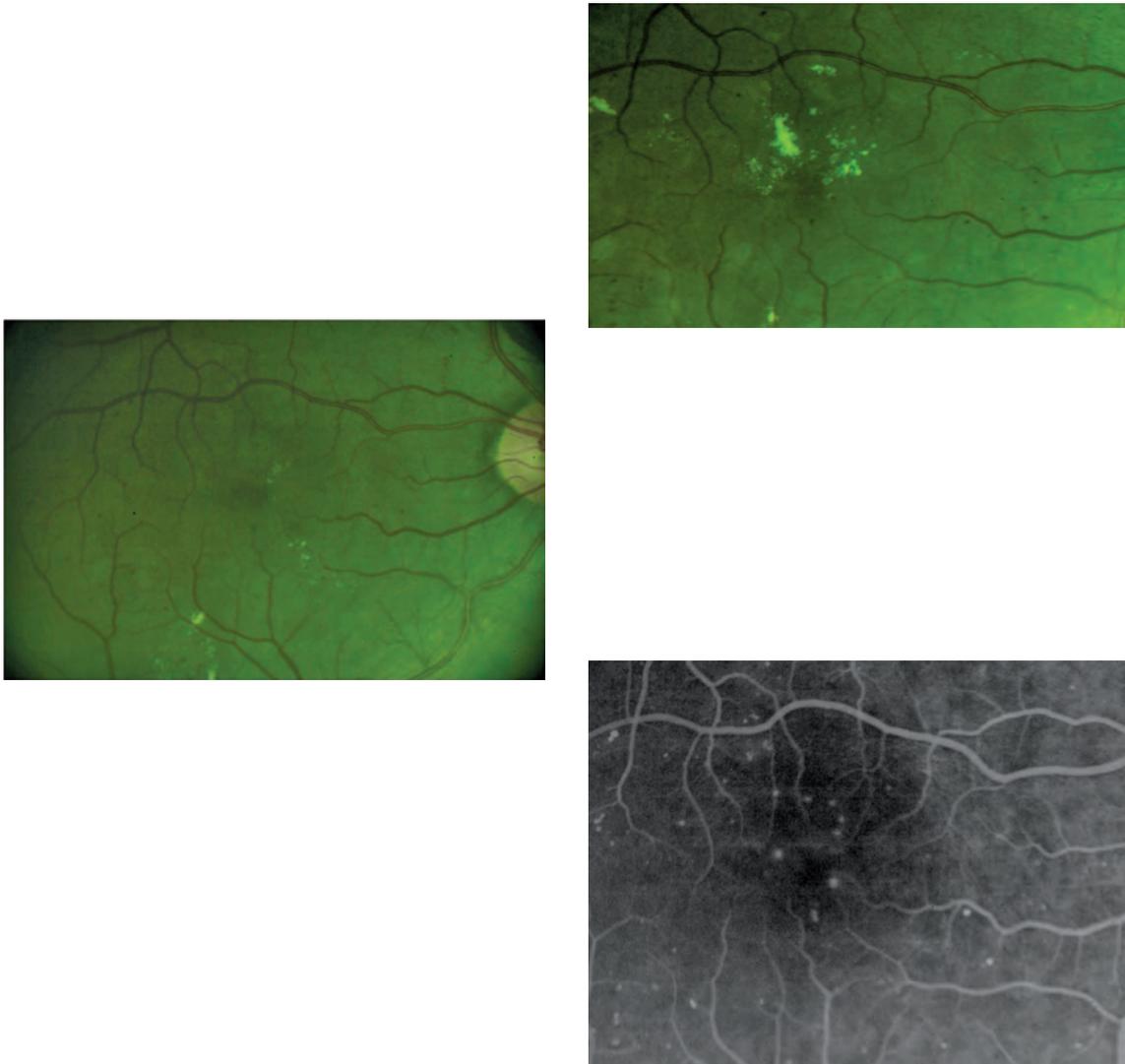


Figure 4: (A) Fundus photograph before (top) and after (middle) SDM for DME. FFA of same eye after SDM for DME (bottom). Note absence of visible laser lesions despite clinical improvement in DME.

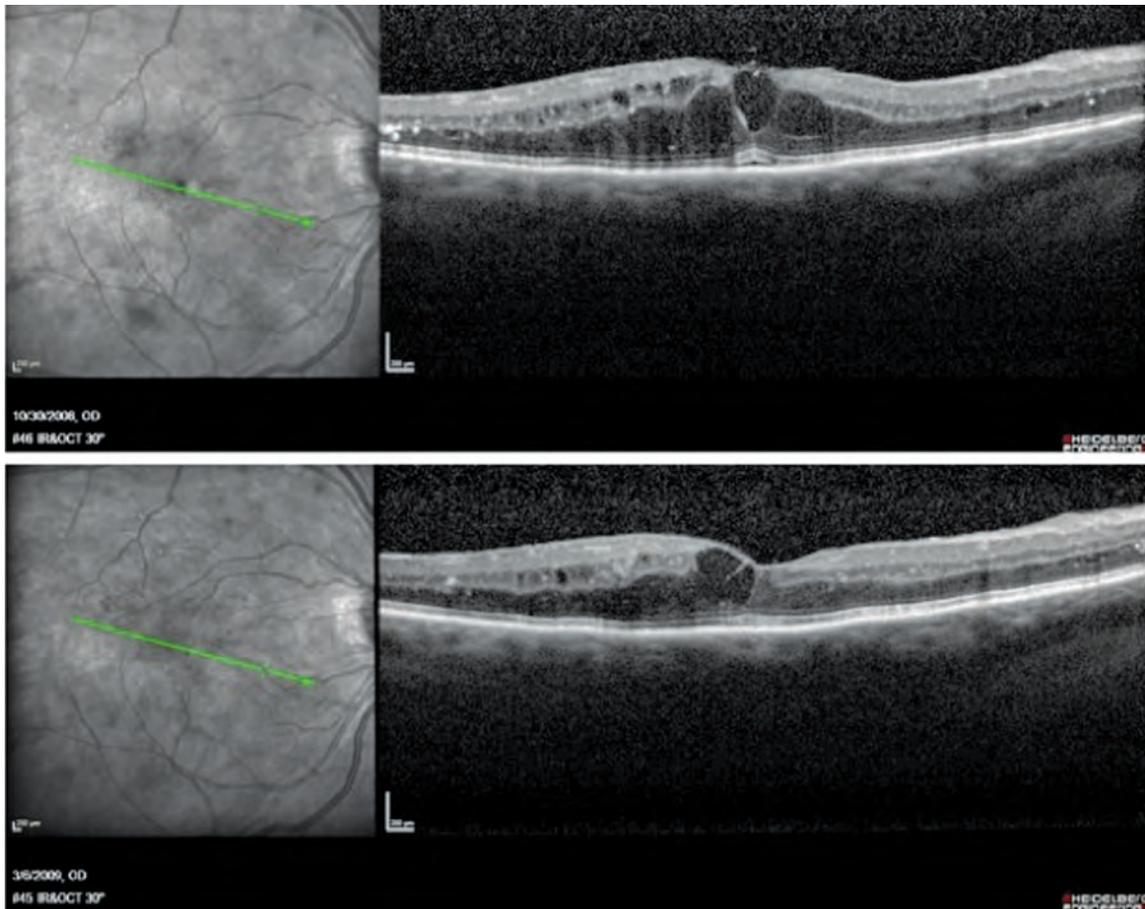


Figure 5: Fourier-domain OCT before and 3 months after SDM. Note improvement in DME and absence of visible laser lesions.

The safety and effectiveness of SDM have been corroborated in subsequent studies of DME.^(36,37) The results of the pilot study reporting SDM PRP effective for PDR await

confirmation.⁽³⁴⁾ From this point forward I will focus on SDM as epitomizing the goals and attributes of SRP for retinal vascular disease.

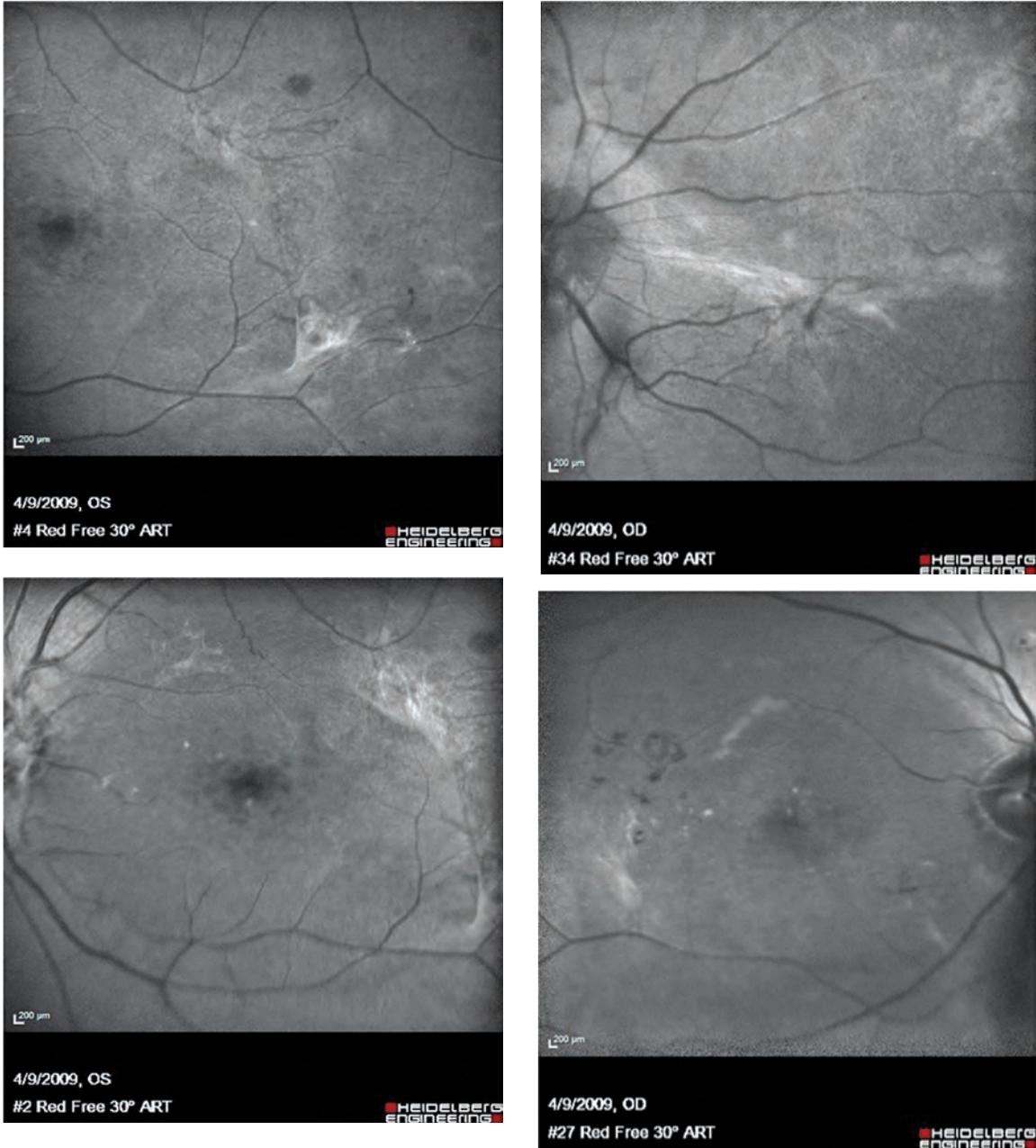


Figure 6: (A) Infra- red fundus photographs

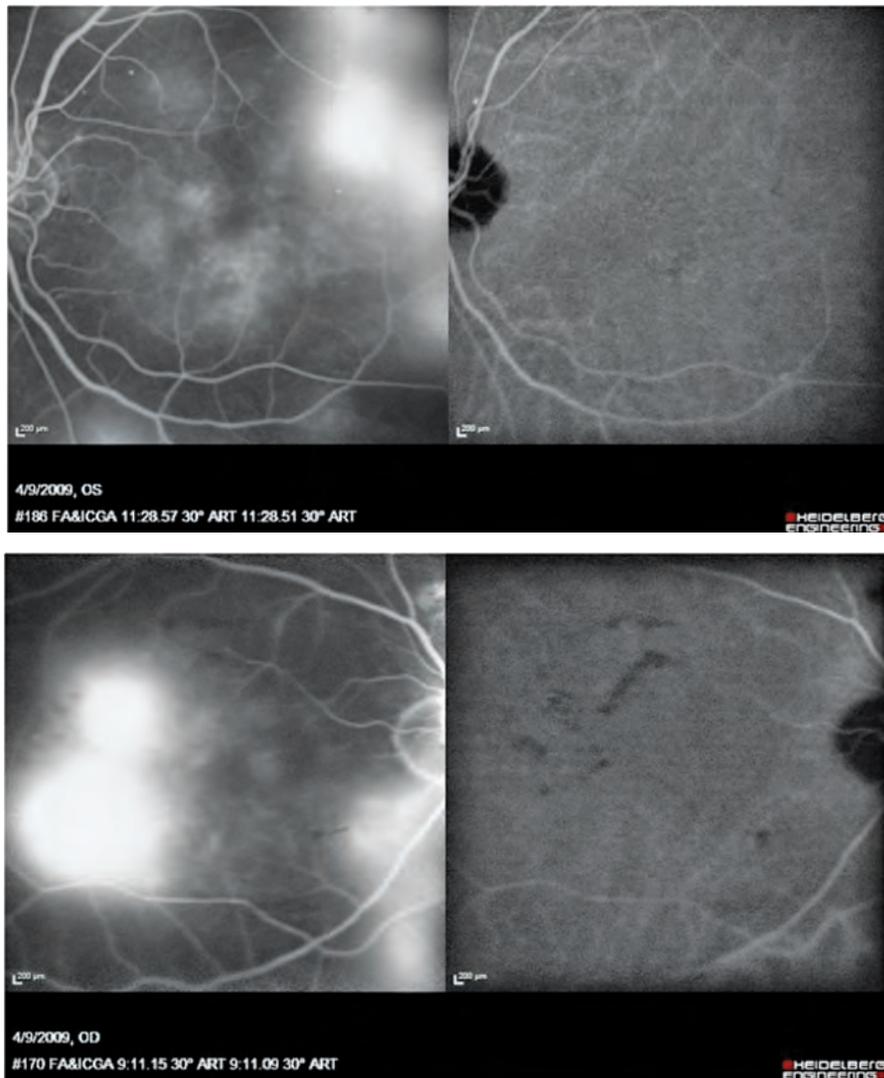


Figure 6: (B) FFA and indocyanine green fundus angiograms of a patient 10 years following SDM for severe PDR and diffuse CSME in both eyes. Post treatment visual acuities = 20/25 OU. Note absence of macular edema and regression of retinal neovascularization. Note minimal pre retinal fibrosis and contraction. Note absence of laser lesions despite over 2,000 macular and 10,000 panretinal SDM applications in each eye. Note persistence of angiographic leakage from macula and retinal neovascularization despite clinically effective treatment.

A Model for Understanding Invisible Endpoint Retinal Photocoagulation

In the absence of precedence for true SRP, the laser parameters employed and reported

in the pilot studies of SDM were selected intuitively and empirically. Despite these limitations, the goals of true SRP were achieved: effective retinal photocoagulation without any retinal damage. Remarkable good fortune, to be sure; but do these results also point

to a rational basis for understanding and optimizing invisible treatment endpoint retinal photocoagulation such as SDM other than the desired clinical effect?

In their pilot study of SDM for DME, Luttrull, Musch and Mainster suggested the American National Standards Institute (ANSI) "Maximum Permissible Exposure" (MPE) concept as a model for understanding true subthreshold, invisible endpoint, retinal photocoagulation such as SDM.⁽³²⁾ ANSI MPE standards are developed from a combination of theoretical and empirical data. The MPE represents the level of laser exposure associated with a 50% risk of a barely visible

(threshold) thermal retinal lesion. For CW laser photocoagulation, that level is approximately 10x MPE. For low DC micropulsed photocoagulation, the corresponding level is 100x MPE. The narrow therapeutic range, together with the heterogeneity of melanin distribution in the RPE, precludes true SRP with conventional CW lasers ("classical SRP"). Conversely, the wide therapeutic range of low DC micropulsed photocoagulation offers the unique opportunity of performing clinically effective (above 0x MPE) and simultaneously true (below 100x MPE) SRP (SDM). (Figure 7) But where in that range do the ideal SDM parameters lie?

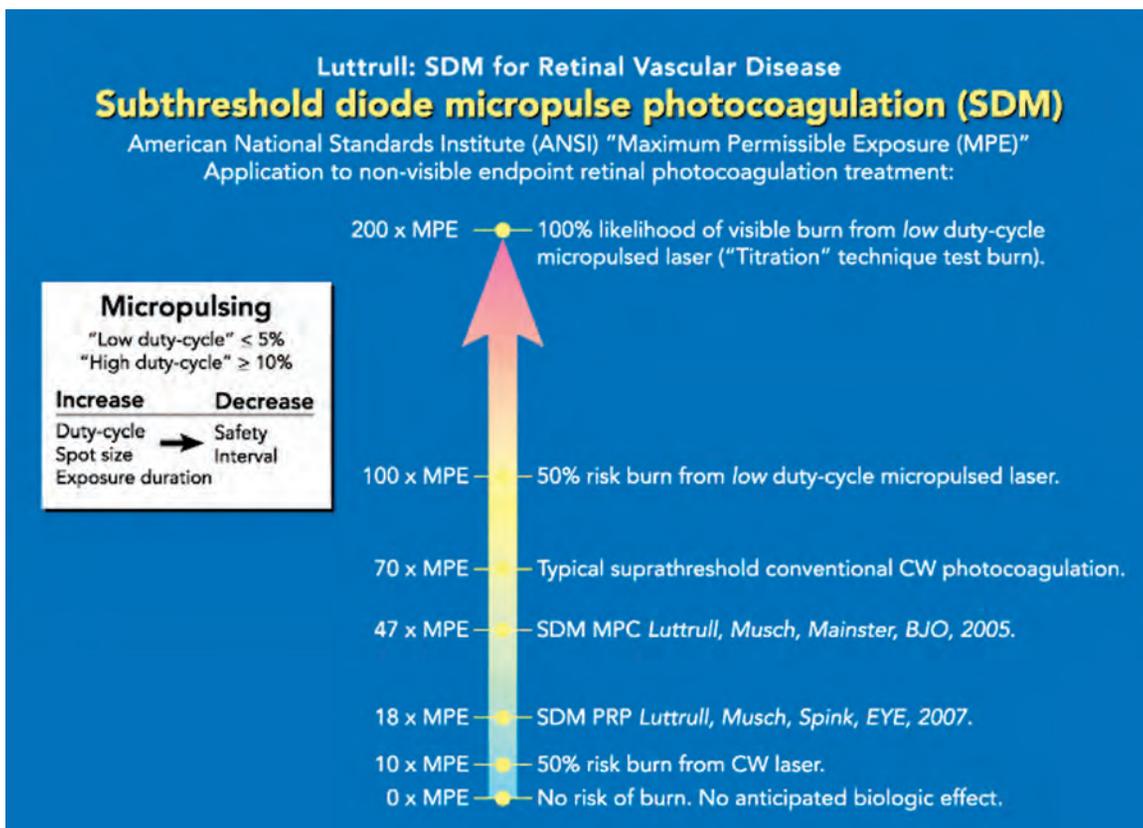


Figure 7: Schematic comparison of American National Standards Institute (ANSI) "Maximally Permitted laser Exposure" (MPE) thresholds for continuous wave and micropulsed lasers.



As stated above, in the absence of precedent, critical laser parameters in the pilot study of SDM for DME were chosen intuitively and empirically, but found to be both safe and effective.⁽³²⁾ Subsequent calculations revealed that the SDM laser parameters in this study produced a laser exposure corresponding to 47x MPE, neatly dividing the interval between no expected biologic effect and a 50% threshold burn risk. In their parallel pilot study of SDM PRP for PDR, Luttrull, Musch, and Spink again reported laser parameters chosen without precedent.⁽³⁴⁾ In this study, retinal irradiance was reduced by use of larger retinal spot sizes and power limitations of the laser to an exposure level corresponding to just 18x MPE. Yet, despite this low level, clinically effective photocoagulation treatment was still observed. The findings of these two pilot studies begin to suggest an ideal therapeutic range for SDM.

Further insight can be gained by analysis of the "titration" approach typically employed in "clinical" SRP. In this approach, a visible suprathreshold micropulse retinal "test" burn is created, generally requiring at least 150 – 200x MPE. The laser power, duty cycle, and / or pulse duration are then reduced by 20 – 50% to produce acutely invisible retinal photocoagulation. Assuming a 50% reduction in irradiance from the test burn level, treatment would then be performed at approximately 75 – 100x MPE. At 100x MPE, the risk of a threshold retinal burn from a MP laser is 50%. Thus, utilizing the "titration" technique to determine MP SRP treatment parameters, a high percentage of latent retinal burns are both predicted and observed. This observation may help further define the ideal SDM

exposure range as that below 75x MPE to minimize inadvertent retinal burns.

Thus, it appears that the ideal parameters for macular SDM may include the following: a small retinal spot size to maximize heat dissipation; a low-duty cycle to prevent heat build up by maximizing thermal relaxation between micropulses; and sufficient power and pulse train duration to achieve laser exposures of approximately 50x MPE. (Table 1, 2) At this level biologic effectiveness is predicted and observed, and inadvertent retinal burns are not. Remarkably, the empirically formulated micropulse laser parameters used to perform

TABLE 1
SDM for Diabetic Macular Edema: Suggested Laser Parameters

<i>Retinal spot size</i>	<i>Duty cycle</i>	<i>Pulse duration</i>	<i>Power</i>	<i>x MPE</i>
131 μ m	5%		0.3 sec	0.95

Table 1. Suggested SDM laser parameters for treatment of diabetic macular edema. 1. Employs a Mainster macular contact lens (magnification 1.05%) (Ocular Instruments) with 125 μ m aerial spot producing a 131 μ m retinal spot. 2. All areas of macular thickening are treated confluent. A typical treatment session requires 300 – 1,000 SDM applications. 3. Use of macular spot sizes greater than 200 μ m and / or duty cycles of more than 10% significantly increase retinal burn risk, particularly in darker fundi.



TABLE 2
SDM for Proliferative Diabetic Retinopathy: Suggested Laser Parameters

<i>Retinal spot size</i>	<i>Duty cycle</i>	<i>Pulse duration</i>	<i>Power</i>	<i>x MPE</i>
400 um	15%	0.05 sec	2.0 watts	33

Table 2. Suggested SDM laser parameters for treatment of proliferative diabetic retinopathy. 1. Employs Volk 160 SuperQuad Panfundus contact lens (Volk, Inc, Mentor, Ohio, USA) (magnification 2.0x) producing retinal spot (400 um) size twice the diameter of the 200 um aerial spot size. 2. In the current recommendations, the reduction in retinal spot size and pulse duration over previously published parameters (34) decreases potential treatment discomfort and burn risk while increasing irradiance and exposure level from 18x MPE to 33x MPE. 3. Typical number of near-contiguous SDM PRP applications for complete fundus treatment is approximately 5,000. 4. PRP is typically performed under topical anesthesia in a single session. 5. Due to the increased retinal spot size with PRP and current diode laser power limitations (2 watts maximum), a 15% DC is employed with PRP to increase the laser exposure level closer to the “ideal” range of approximately 50x MPE. While a 15% DC increases the risk of inadvertent retinal burns, the risk is very small except in darkly pigmented fundi, and far less potentially catastrophic compared to creation of inadvertent macular burns. In darker fundi, pulse envelope duration and / or duty cycle may be reduced to maintain patient comfort and / or reduce risk of inadvertent retinal burns.

SDM in the pilot study of DME treatment fortuitously approximate the ideal suggested by the ANSI MPE model. Correspondence between this calculable model and clinical findings may thus provide a reasonable basis for rational assessment of invisible endpoint retinal photocoagulation parameters in order to optimize treatment outcomes.

Subthreshold Retinal Photocoagulation and Current Concepts of Retinal Vascular Disease

The effectiveness of SDM calls into question all theories of retinal laser action that invoke as necessary the creation of chorioretinal scarring by thermal retinal destruction.⁽¹⁶⁾ Instead, by exclusion SDM would appear to operate by laser - induced modulation of RPE cytokine production. This theory is consistent with

current understandings of the pathogenesis of retinal vascular disease, and is supported by clinical observations and laboratory studies.⁽³²⁻³⁹⁾

Clinically Significant vs. OCT DME

Current guidelines for treatment of DME were defined by the EDTRS, based on bio-microscopic findings and accounting for the risks of conventional suprathreshold macular photocoagulation. However, OCT now allows clinicians the ability to diagnose DME well below “clinically significant” macular thickening levels. The remarkable safety profile of SDM may make it uniquely suited to the treatment of OCT visible DME not meeting the ETDRS “clinically significant” threshold. As observed in the management of many other



disease states, such as early treatment of DME may ultimately improve patient outcomes.

SDM: Clinical Observations

With ten years of clinical experience using SDM treatment as the exclusive laser modality for the treatment of retinal vascular disease, the author offers the following clinical observations:

- Due to the absence of retinal damage, SDM can be repeated as necessary over time to achieve the desired treatment effect, much like administration of a drug.
- Clinical improvement may continue slowly over a long period of time, thus retreatment is generally reserved for disease that fails to respond to initial treatment, or recurs.
- Serial OCT (for DME) and fundus photography (for PDR) are very helpful in monitoring treatment response (Figures 8 & 9). DME

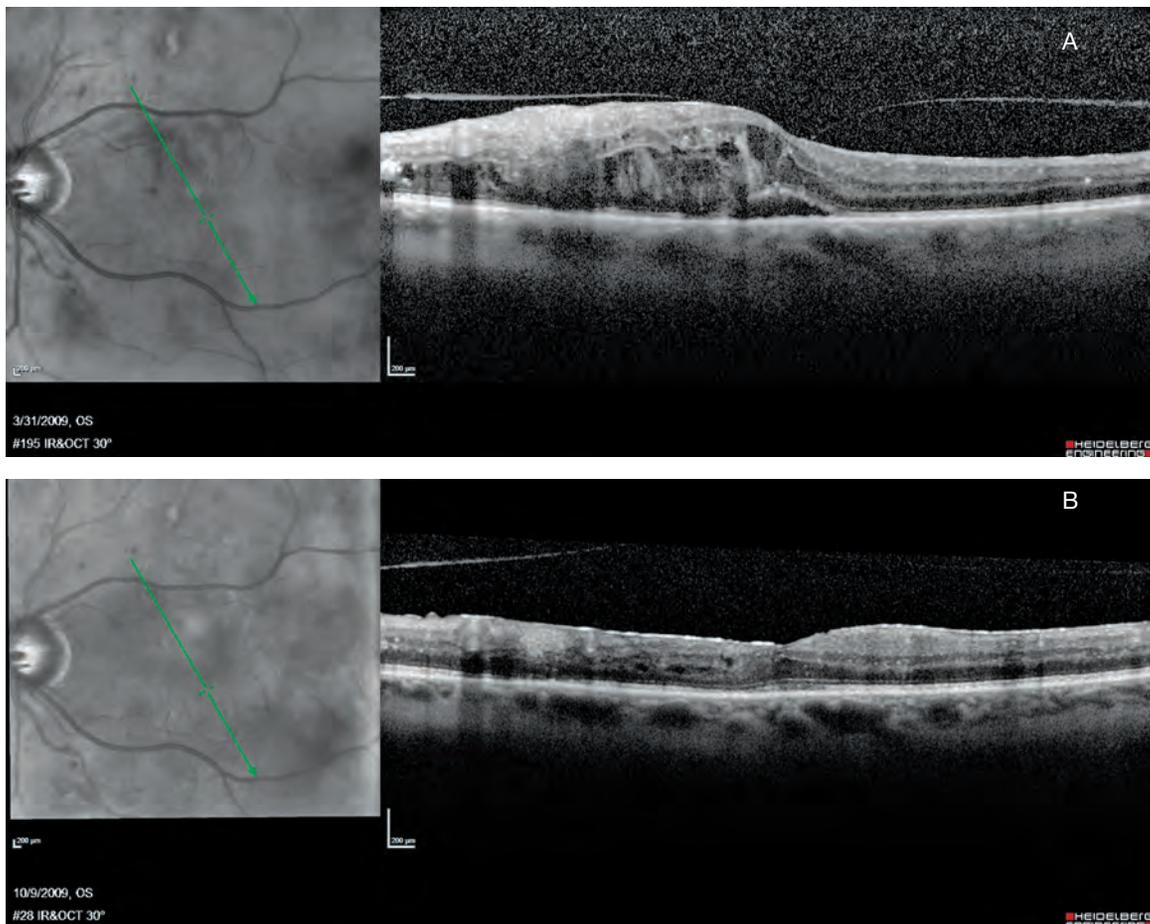


Figure 8 (A-B): Comparison of clinical courses of improvement in DME following SDM demonstrated by Fourier domain OCT: (A) Patient A before (top) and 3 months following (bottom) single session of SDM.

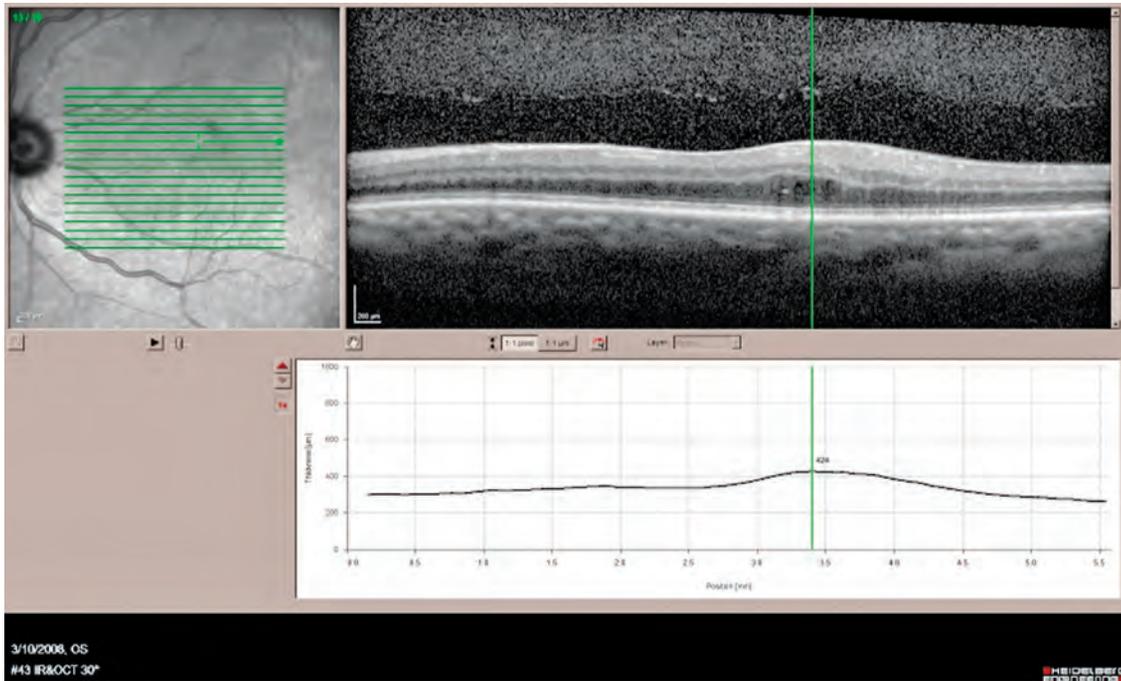


Figure 8 (B1):

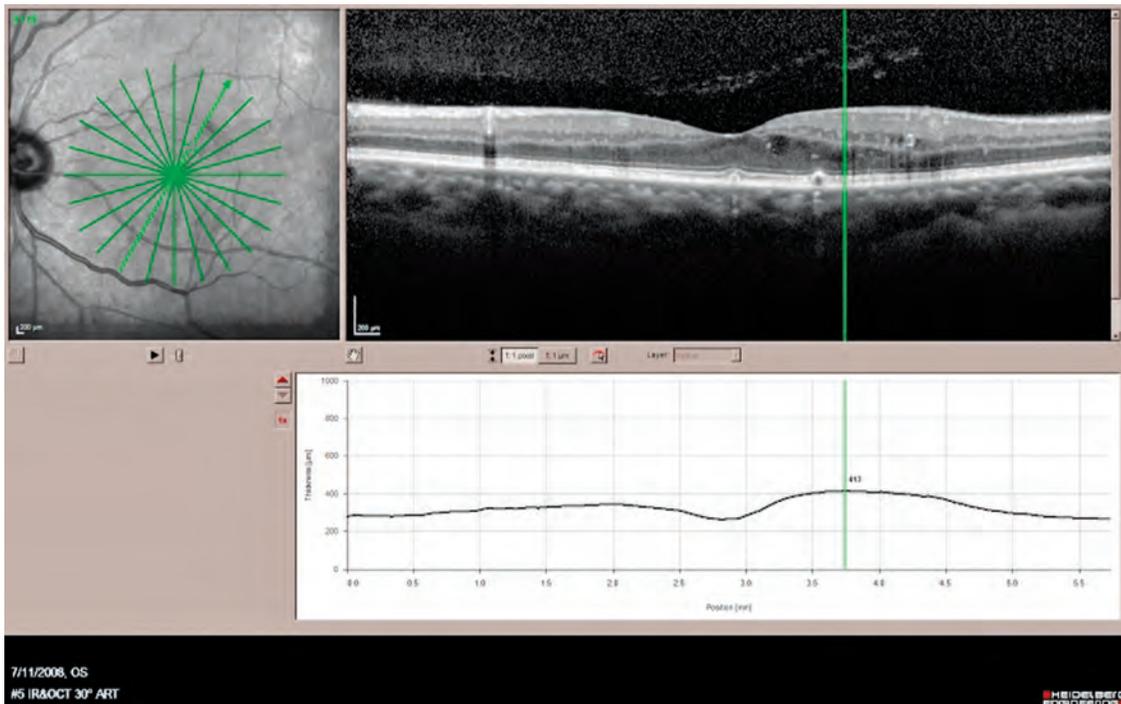


Figure 8 (B2): Three months post SDM, DME little changed.

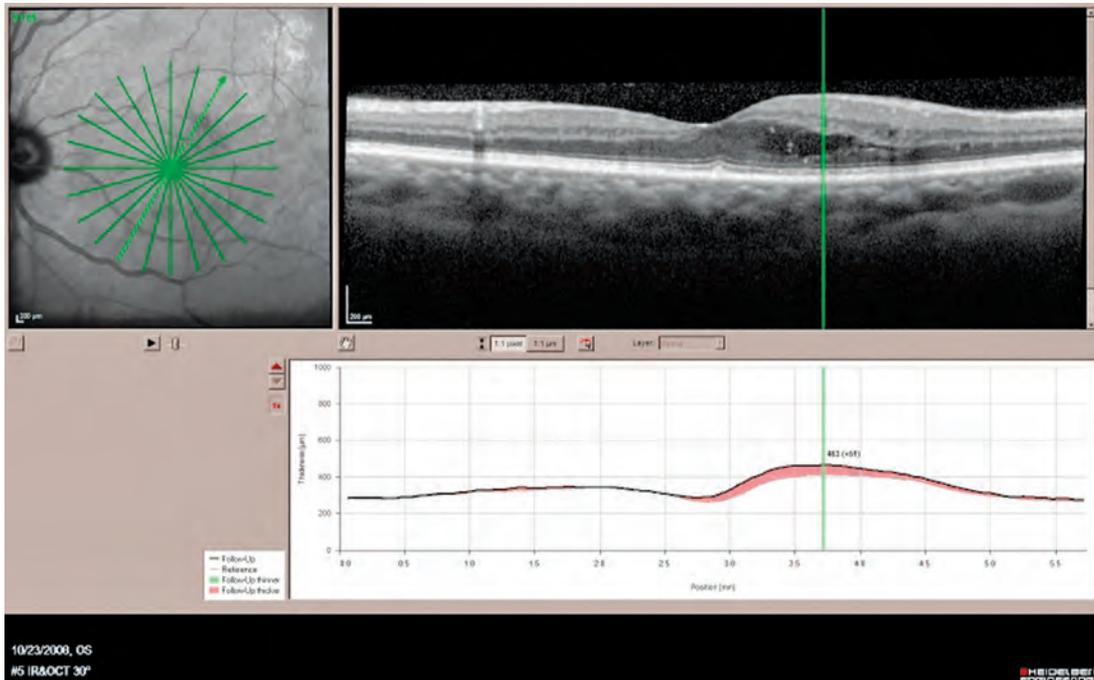


Figure 8 (B3): Six months post SDM. DME worsened; SDM repeated.

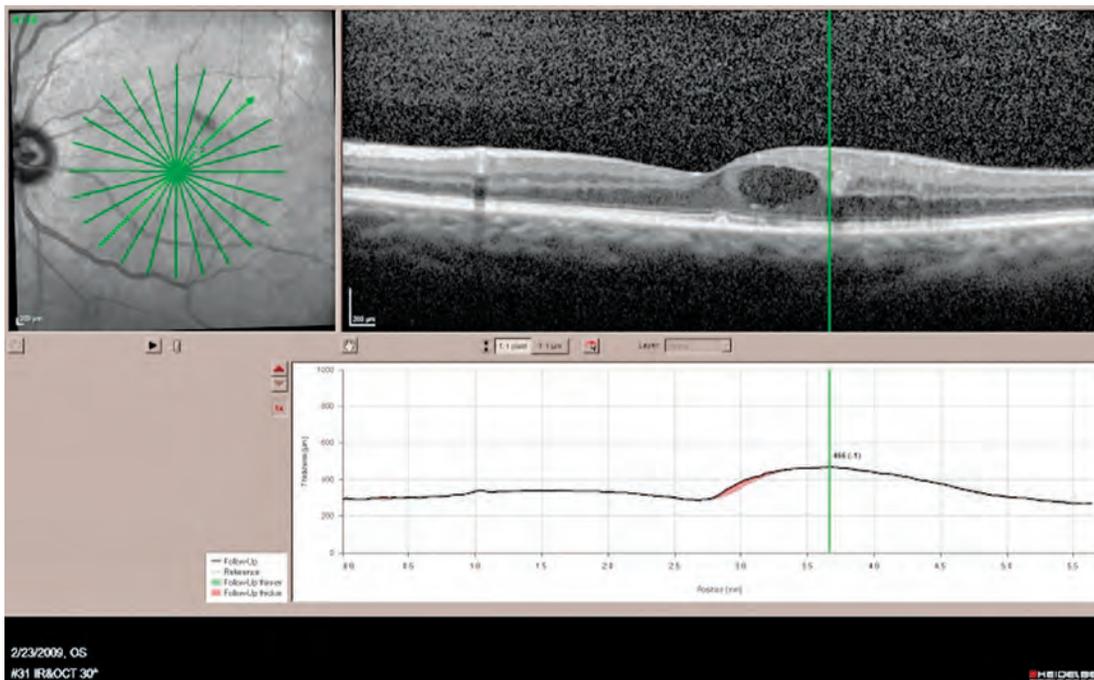


Figure 8 (B4): Nine months post initial SDM. DME unchanged. SDM repeated.

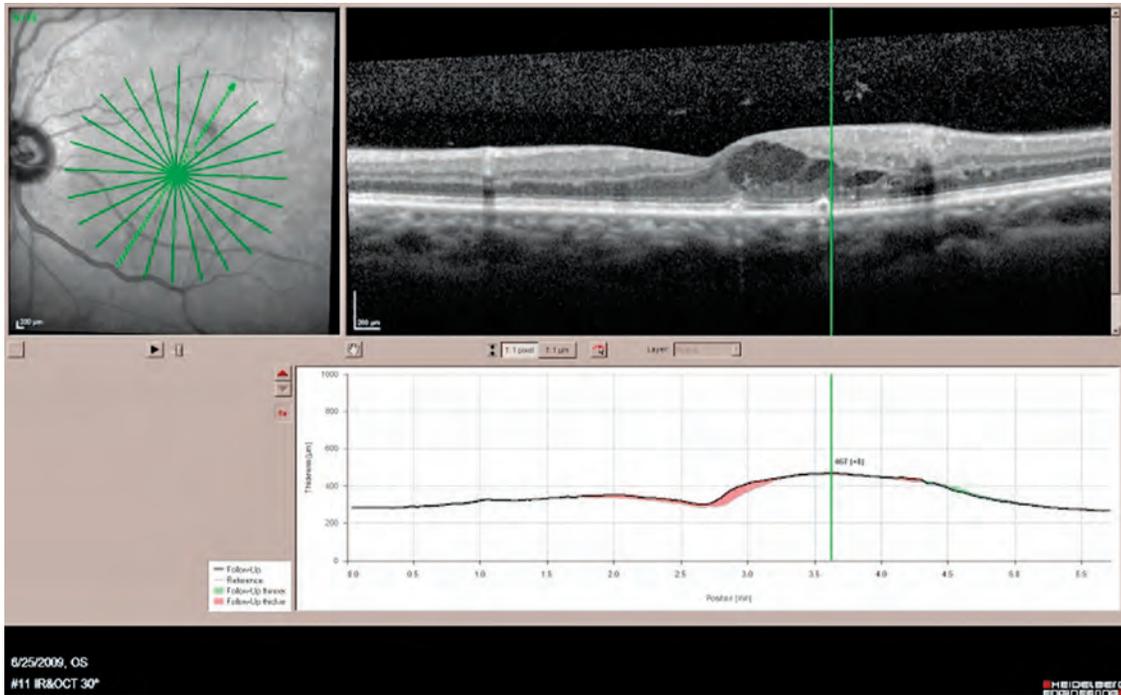


Figure 8 (B5): One year following initial SDM. DME unchanged.

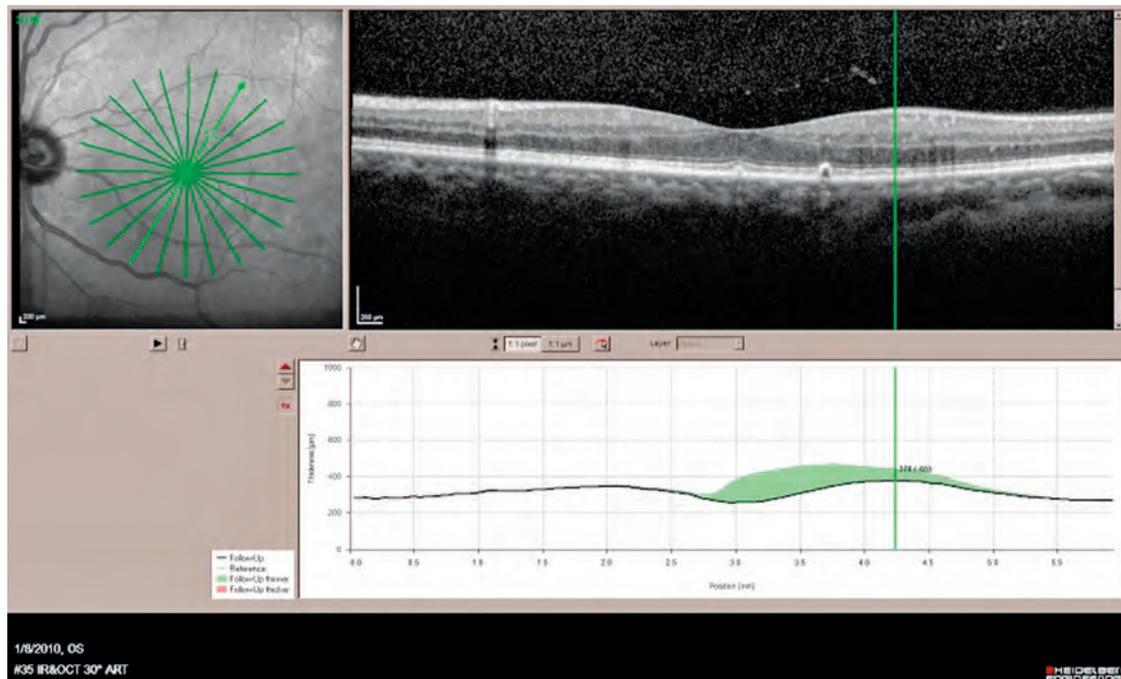


Figure 8 (B6): Fifteen months post initial SDM and 6 months post most recent SDM. DME resolved.

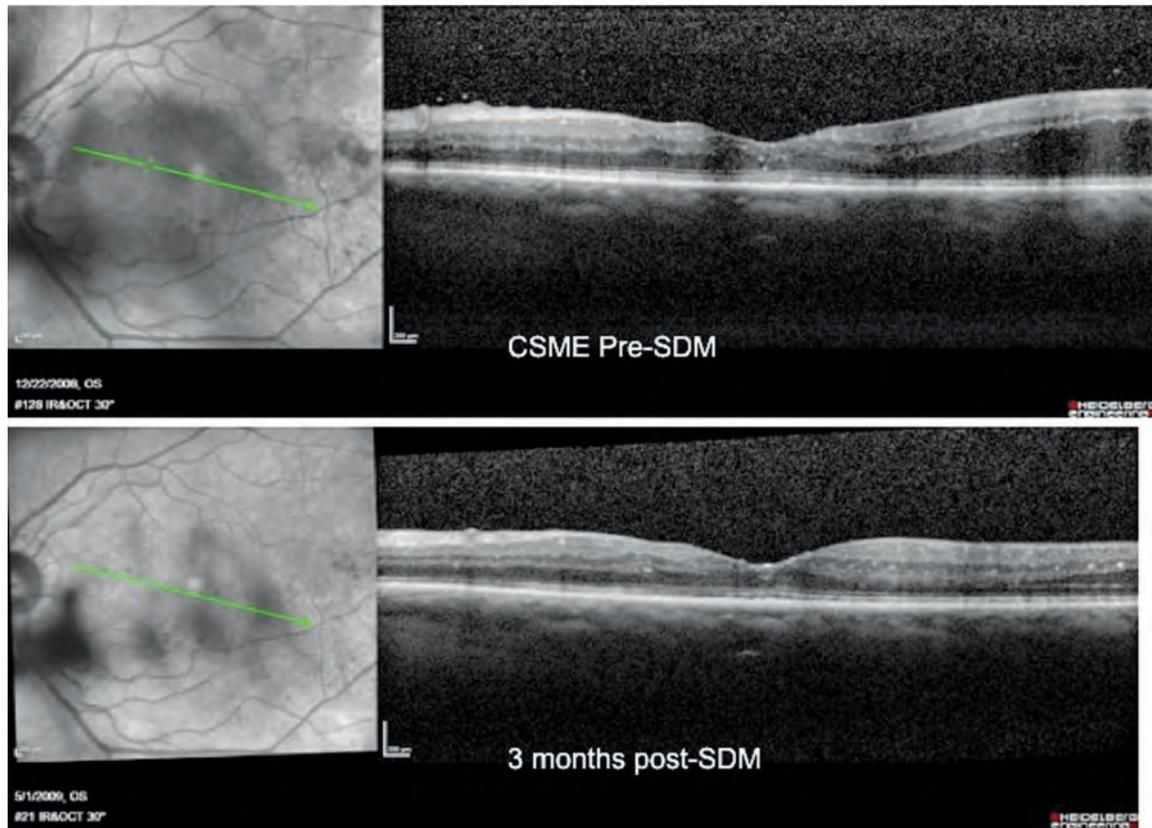


Figure 8 (C): Patient C before (top) and 3 months after (bottom) single session of SDM for DME.

DME may recur following SDM, as reported by Sivaprasad and associates.⁽²⁸⁾ Such recurrence is consistent with the proposed theory of action of SDM and permitted by the absence of treatment-induced chorioretinal scarring^(28, 32 - 34, 40) (Figure 9). Recurrent DME following SDM may be successfully retreated without retinal injury.

- In patients with dark fundi, reduction in laser irradiance may be prudent to avoid inadvertent retinal burns. Although alterations in various laser parameters such as spot size, power, DC, and pulse envelope lead to

linear changes in exposure level, the clinical effects of such changes are not linear, but logarithmic in character due to tissue effects.

- Clinical experience demonstrates that, for treatment of DME, increasing retinal spot sizes to 200 μ m or more, and / or DC beyond 5% may significantly increase retina burn risk even if total irradiance and exposure level in xMPE remains unchanged. (Figure 10)

- The 810nm diode laser wavelength penetrates media opacities such as nuclear sclerotic cataract, vitreous hemorrhage and intraretinal hemorrhage easily. Because it is

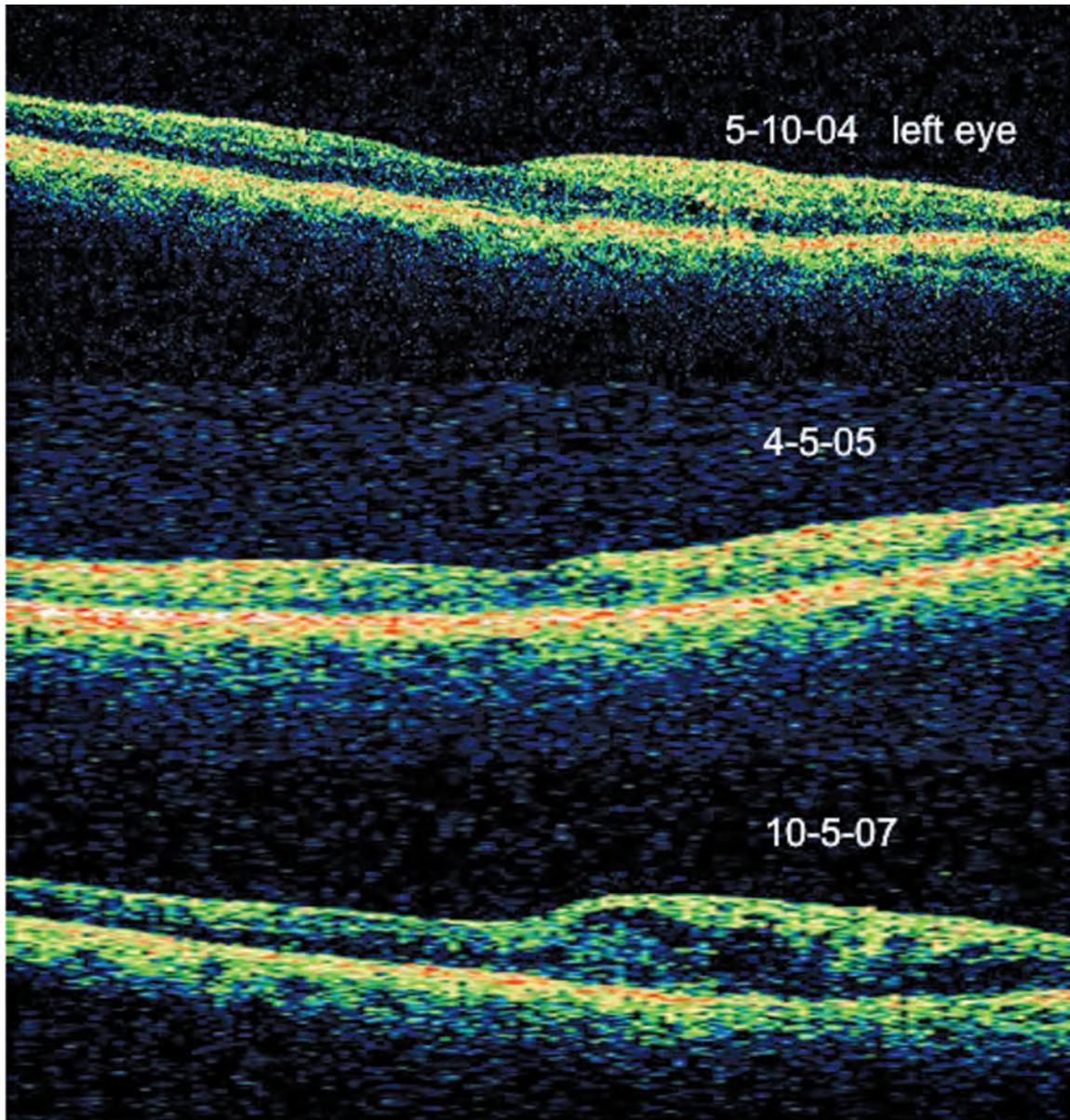


Figure 9: Recurrent DME following SDM performed 5-10-04.

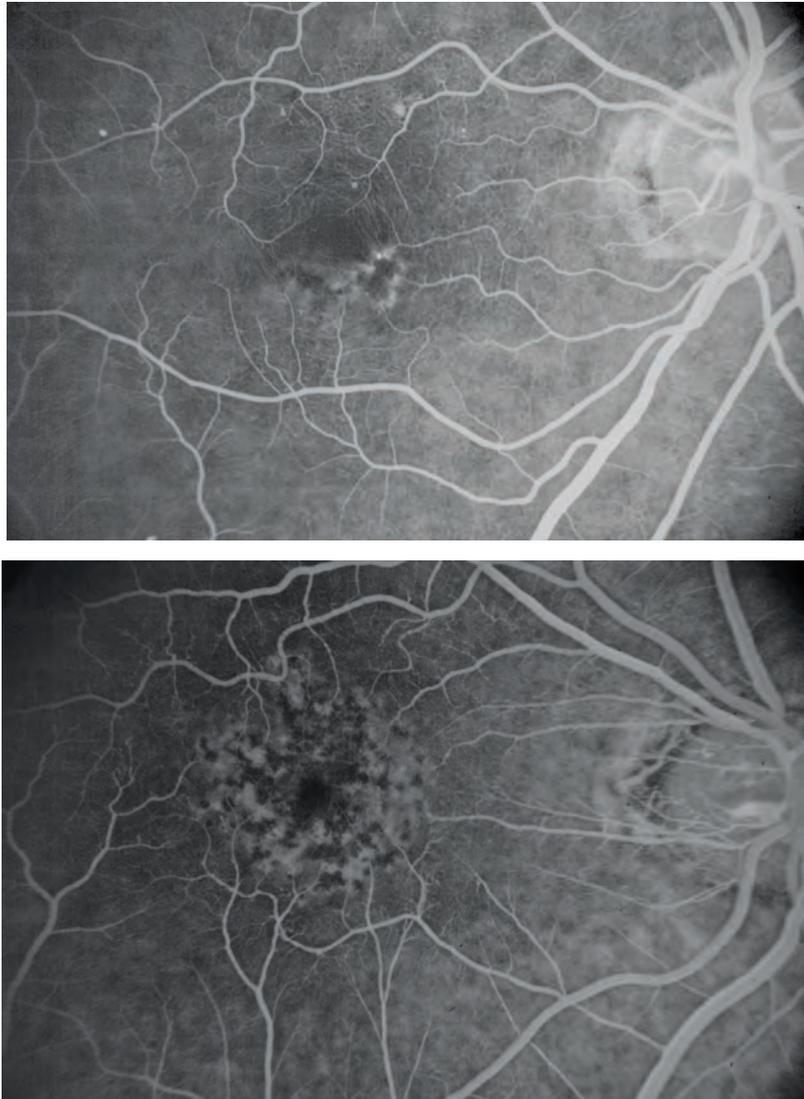


Figure 10: Inadvertent macular burns following micropulsed diode macular photocoagulation demonstrated by FFA in 2 patients. These burns developed despite subthreshold diode micropulse photocoagulation parameters producing 43 x MPE (patient A) and 57 x MPE (patient B), well within the “ideal” range for SDM. In both cases, the fundi were dark, and higher duty cycles of 10 and 15% were employed, with reductions in pulse envelope to 0.15 second to maintain the xMPE at about 50. Most eyes treated with micropulse duty cycles of 10 to 15% do not suffer inadvertent retinal burns. However, these cases illustrate: a) the non-linearity of tissue response to linear changes in micropulse laser parameters; and, b) the importance of using a 5% duty cycle to insure complete avoidance of thermal retinal injury when employing high-density treatment (SDM). Encroachment on the thermal relaxation time of retinal melanin appears to occur rapidly beyond the 5% duty cycle level, rapidly increasing the burn risk above this duty cycle level. A similar but less marked logarithmic increase in burn risk occurs with linear increase in retinal spot size due to less efficient heat dissipation in the central portion of the retinal laser spot. In the author’s 10 years of experience with SDM no inadvertent retinal burns have been observed with the suggested macular SDM treatment parameters (Table 1) employing a 5% DC and 125 μ m spot size.



not absorbed by neurosensory retina, SDM laser parameters do not have to be adjusted for macular swelling; however, when treating markedly thickened retina care should be taken to focus the aiming beam at the level of the RPE.

Unlike conventional photocoagulation, pain with SDM increases with increasing spot size for a given irradiance level, and to a lesser degree power and duty cycle. Unlike conventional CW photocoagulation, with SDM PRP the patient pain threshold is significantly lower than the retinal burn threshold, permitting patient comfort to inform SDM PRP treatment parameters.⁽⁴⁰⁾

Despite clinically successful SDM treatment, angiographic leakage may continue little changed in the macula following treatment of DME, or from NV in the treatment of PDR. In this respect SDM is not unlike conventional photocoagulation, or even pharmacologic therapy, although in the absence of background chorioretinal scarring such leakage may be more easily appreciated. Persistent angiographic leakage does not indicate treatment failure (Figure 6).

SDM does not elicit any inflammatory response. The significance of this fact clinically cannot be overstated. The effect of the absence of treatment associated - inflammation is particularly notable in the treatment of PDR. Not only are all complications associated with post treatment inflammation absent, but the postoperative clinical appearance and course are altered significantly compared to conventional suprathreshold photocoagulation. SDM PRP

does not cause or exacerbate DME. Fibrosis and contraction of pre retinal fibrovascular membranes is minimal, reducing the risk of retinal traction, vitreous detachment, and vitreous hemorrhage. (Figures 4 - 6 & 11) The clinical picture following SDM treatment for PDR recalls the clinical picture 6 - 8 weeks following intravitreal injection of a vascular endothelial growth factor (VEGF) inhibitor, only developing more slowly. As noted in the DRS, arrest or regression of NV is the rule, with disappearance rare. This treatment response has been noted to be emblematic of VEGF inhibition.⁽⁴¹⁾

SDM, whether for DME or PDR, is performed with topical anesthesia alone in a single session. Patients experience no bright painful light flashes, or pain, visual loss or other visual disturbance following treatment. Patients with DME often report subjective visual improvement within days following SDM. Patient compliance with SDM is thus excellent.

Combination Therapy

SDM can be combined with drug therapy to achieve management of retinal vascular disease without retinal damage. Because the effects of photocoagulation for retinal vascular disease tend to be slow in onset but lasting in effect, while drugs tend to take effect and wear off quickly, SDM and pharmacologic therapy may be complementary and potentially synergistic. However, the optimal timing and sequencing of SDM with augmentary pharmacologic therapy is unknown.

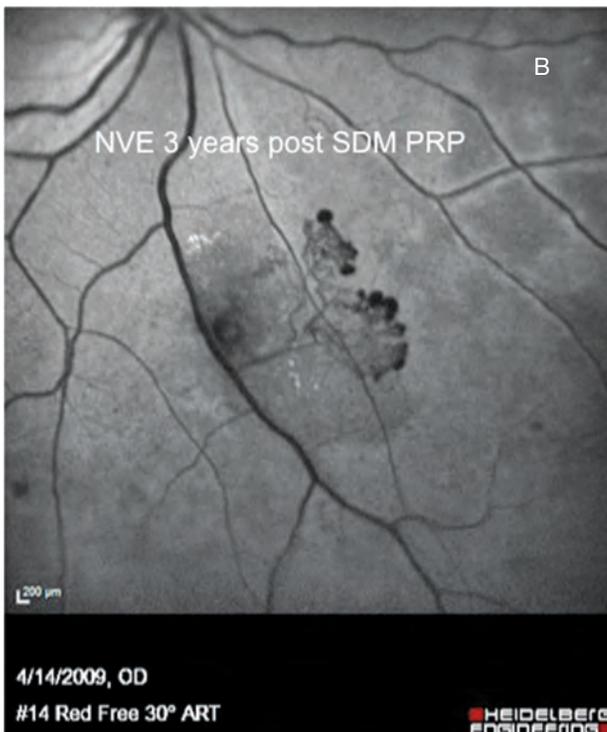
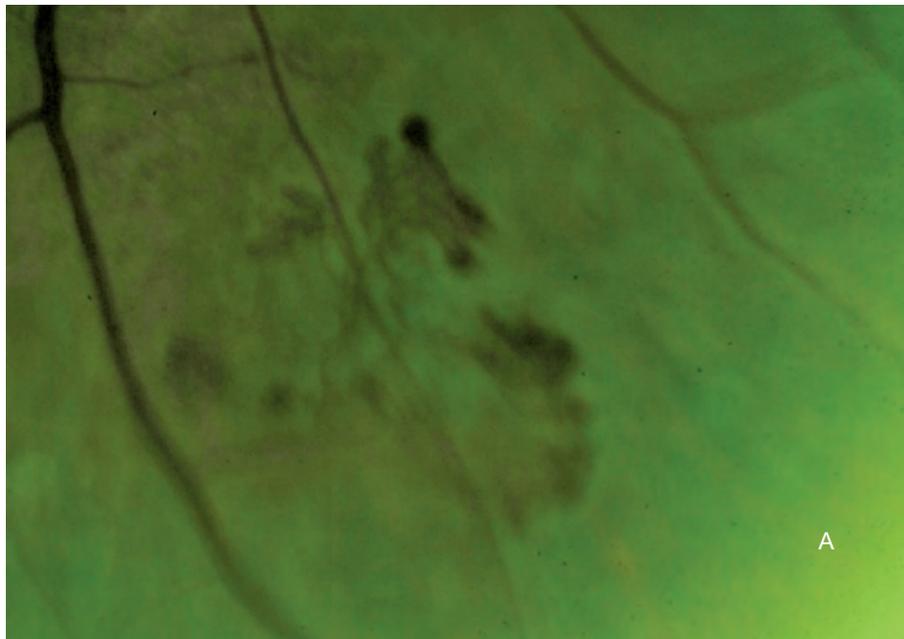


Figure 11: Retinal neovascularization at presentation (A) and 3 years following SDM PRP (B): Note lack of progression, distal shunt formation, and absence of pre retinal fibrosis and chorioretinal scarring.



Other Disease Applications of SRP

SRP has been reported effective for other diseases including macular edema complicating branch retinal vein occlusion, and central serous chorioretinopathy.^(42,43)

The Future of SRP

SRP is an area of active investigation. Because of the invisible treatment endpoint with true SRP/SDM, new imaging and documentation techniques would be useful. The large number of laser applications and treatment safety suggests that SDM would be ideal for incorporation into a fully automated, OCT – guided, application system.

Summary

SRP, epitomized by SDM, represents the natural evolution of photocoagulation treatment for retinal vascular disease foreshadowed in findings from the DRS and ETDRS. At the same, SDM represents a significant departure from conventional treatment techniques and expectations, and the conventional wisdom regarding the mechanism of action of laser photocoagulation for retinal vascular disease. In subthreshold photocoagulation for retinal vascular disease, epitomized in SDM, our understanding of disease pathophysiology is improved; the benefits of treatment are maximized; and the promise to our patients to “First, do no harm” is fully realized.

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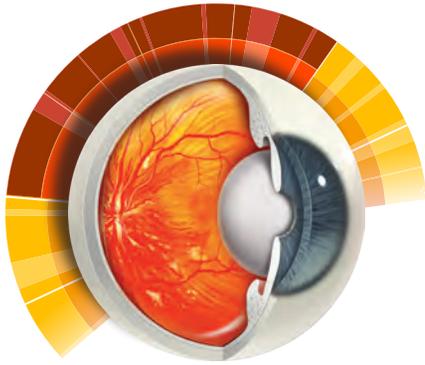
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8

Laser Treatment for Retinal Holes, Tears and Peripheral Degenerations

FEDERICO A. GRAUE-WIECHERS, MD.,
NATALIA SALDAÑA-VERDUZCO, MD

Introduction

The role of prophylactic treatment of peripheral retinal degenerations that pose a higher risk for rhegmatogenous retinal detachment (RD) has been poorly understood. Despite their high incidence there are only a few controlled trials that determine which lesions are suitable for therapy. This has developed in excessive and unnecessary laser treatment.

In order to learn which lesions can represent a real risk for developing retinal detachment and when to treat them we first have to consider every fact involved in the physiopathology of retinal detachment.

Vitreous condition is crucial. The role of a chorioretinal scar produced by laser or cryotherapy must be clear in order to know what to expect from treatment.

During this chapter we will first examine the vitreous gel and its changes through the aging process, the peripheral retinal degenerations and their implication in retinal detachment, the different treatment options and finally the pathological situations that increase the risk of having a RD.

Physiological Mechanisms of Retinal Adherence

During the embryonic stage of retinal formation, as the optical vesicle invaginates to form the optic cup, two epithelium contact each other: the neurosensory epithelium which will give rise to the nine internal retinal layers, and the epithelium which will develop the retinal pigmentary epithelium. This attachment lacks union complexes that allow a strong adherence between them, so this constitutes a virtual space that becomes real if fluid of any source splits them. This



led to the assumption that this union is enhanced by physiological vascular mechanisms: Choroidal osmotic pressure, hydrostatic pressure of retinal vessels and active transport of substances through the RPE. These three factors are known as the choroidal pump.¹

Fluid is constantly produced in the ciliary processes in normal conditions, this maintains a stable intraocular pressure which partly drains through the trabeculum, and a smaller part travels through the vitreous, since it is hypo-osmolar, and flows downstream towards the choroid and never upstream.

The second factor, takes place in the retinal capillaries by fluid exchange between arterial and venous branches by hydrostatic pressure.

The active transport of substances through the RPE is the third fact, and it allows molecules and fluid absorption through the retina draining them towards the choroid.

The optimal functioning of these three factors allows the retina to maintain attached and transparent.

The vitreous has nothing to do with retinal attachment as thought before. In eyes with previous vitrectomy, the retina is able to keep attached with no vitreous present.

Intraocular Currents and Vitreous Traction

The choroidal pump is a powerful tool that keeps the retina in its place, but there

are forces that act against it: Intraocular currents, and vitreous traction over the retina.¹

With the aging process the vitreous changes into a syneretic liquid state. Currents are formed in the vitreous cavity that with saccadic movements and in the presence of a retinal break will make the liquid vitreous pass to the potential space between the retinal pigmentary epithelium and the rest of the retina.

Vitreous traction upon the retina is strong, and during acute posterior vitreous detachment (PVD) can cause a retinal tear at sites of pathological vitreous attachments.

Vitreous Liquefaction

Vitreous aging (synchysis senilis) consists in liquefaction (syneresis), the initial event takes place in front of the macular area or in the center, with formation of liquid cavities inside the vitreous gel, which tend to coalesce because of progressive degeneration of collagen fibers and hyaluronic acid macromolecules.^{1,2}

These changes are directly age related. It is known that only 9% of patients under 20 years show liquid cavities inside the vitreous gel compared to 90% of patients over 40 years old. This increase in liquefaction during aging is not related to a reduction in the amount of collagen or hyaluronic acid, thus their concentration in the vitreous rises.



There are many facts that can accelerate the synergetic process in the eye: myopia, trauma, intraocular inflammation, eye surgery or hereditary syndromes.

Posterior Vitreous Detachment (PVD)

Posterior vitreous detachment is strongly related to syneresis. Only a small amount of liquefaction is tolerated by the vitreous before it separates from its posterior attachment.³ Once the vitreous is liquefied, at some point a break develops in the posterior cortical vitreous, through which the liquefied vitreous passes abruptly into the subhyaloid space, this separates the posterior hyaloid from the retina and progresses anteriorly towards the vitreous base where it remains attached.

This event usually takes place in patients age 50 or older, even when many patients do not report acute symptoms, most will describe photopsias from physical stimulus of vitreoretinal traction and floaters caused by vitreous opacities such as blood or aggregated collagen fibers. Patients with these symptoms should be seen promptly, specifically looking for retinal breaks that could have taken place during posterior vitreous detachment. Some patients may suffer rupture of retinal vessels and vitreous hemorrhage, or a slight retinal hemorrhagic trace.

From all the facts associated with retinal detachment this is probably the most important.

Vitreoretinal Attachments

Normal vitreous is firmly attached to some areas of the retina. The strongest attachment takes place at the vitreous base^{2,4} which is a circumferential zone located 5 mm behind the limbus straddling the ora serrata, measures approximately 6mm, and extends 2mm anterior and 4 mm posterior to the ora.

The second strongest attachment is located at the margin of the optic disc. When PVD occurs the ring of attachment (Weiss ring) can be identified by ophthalmoscopy floating in the vitreous above the optic nerve head and may be accompanied by vascular ruptures and vitreous hemorrhage.

Finally there are other normal attachments, not as strong as the ones mentioned before, at the veins located in the mid-periphery of the retina.

Abnormal attachments of the vitreous can be found in chorioretinal scars or peripheral degenerations such as lattice, because of its clinical significance this will be discussed separately.

Peripheral Retinal Lesions

There is a great variety of anatomic variations and degenerations in the retinal periphery, some of them lack clinical significance since they do not play a causative role in the development of RD (Table 2). Thus it is important to understand, recognize



and distinguish these lesions from those that predispose a retinal detachment so the need of treatment or observation can be established (Table 1).

Table 1

PERIPHERAL RETINAL LESIONS	ASSOCIATION WITH RD. %	FOUND IN RD. %	PREVALENCE IN ADULT POPULATION
LATTICE DEGENERATION	2-4%	30%	8%
CYSTIC RETINAL TUFT	0.28%	10%	5%
SENILE RETINOSCHISIS	0.05%	2.5%	7%

Next we will group the lesions according to their clinical behavior in order of importance:

Lesions Predisposing to Retinal Detachment

1. Lattice degeneration
2. Cystic retinal tuft
3. Degenerative (Senile) retinoschisis.
4. Trophic retinal holes
5. Retinal tears
6. Dialysis

1. *Lattice Degeneration*

This is the most important among peripheral retinal lesions, it has been associated

with a 20-30%⁵ incidence of rhegmatogenous retinal detachments. This was first described in 1930 by Jules Gonin⁶, and it was until 1952 that Schepens⁷ designated this entity. Hystologically (Figure 1) consists of localized retinal thinning overlying vitreous liquefaction, with strong vitreoretinal attachments at the margins of the lesion⁸.

The pathogenesis of lattice is still unknown.

Often they are located anterior to the equator, in the vertical meridians and the inferior quadrants, and found bilateral between in 30-50% of patients. Its incidence is higher in myopic patients, occurring in 15% of eyes with axial length of 30mm or more⁹. This degeneration can be found in 10-35% of eyes with a collateral retinal detachment.¹⁰



Figure 1: Lattice Degeneration (Courtesy: Dr. Oliver Schneider).

There are very interesting variations in the appearance of lattice degeneration: white lines, snail tracks, various degrees of pigmentation, presence of holes or tears.

The main danger in lattice takes place during posterior vitreous detachment formation, since retinal tears can form from vitreous traction; these tears have been found associated to lattice in 1.5%.¹¹ Because of its association with retinal detachment this is a good combination of facts to consider prophylactic laser treatment.

Holes have been described in lattice degeneration in 16-24%,⁹ and in the presence of posterior vitreous detachment they have been associated to retinal detachment. Approximately 2.8% of rhegmatogenous retinal detachments are due to retinal holes within a lattice,¹² this represents a low risk in order to justify prophylactic treatment.

2. Cystic Retinal Tuft

These are elevated vitreoretinal lesions, small, round or oval, sharply circumscribed and have chalky-white color.

Histologically consist of dense accumulations of glial tissue in small nodules on the surface of the retina, enclosing crypts of formed vitreous intimately attached to the overlying vitreous,¹³ often have been associated with pigmentation and trophic changes in the adjacent retina.

They are commonly associated with retinal tears, and it has been estimated that up to 10% of retinal detachments are caused by retinal tears in areas of cystic retinal tufts.¹⁴ It has also been established in autopsy reports that they can be found in 5% of the population.

The risk of developing retinal detachment from a cystic retinal tuft is 0.28% so their prophylactic treatment is not indicated.¹⁵

3. Degenerative (Senile) Retinoschisis

Was first described in 1933 by Bartels¹⁶ as an idiopathic degenerative process which clinically presents as a peripheral, smoothly elevated lesion with a convex posterior border. It is frequently asymptomatic bilateral and located in the inferior temporal quadrants.

During ophthalmoscope, examination and scleral indentation can be differentiated from a retinal detachment because it has a "white with pressure" sign.



By histopathology this lesion begins in the outer plexiform or inner nuclear layer of the peripheral retina as a degeneration of neuroretinal and glial supporting elements. Gradual accumulation of mucopolysaccharide causes it to enlarge (Figures 2, 3).

When breaks are found in the external layers a retinal detachment can develop. Retinoschisis is present in up to 6% of retinal detachments, but is responsible only for less than 2.5%.¹⁷

The natural course of this type of lesions does not show progression therefore treatment must be limited to progressive symptomatic cases with associated retinal detachment.

Laser demarcation treatment or treatment of the holes within a retinoschisis should be avoided since it has been associated with severe complications such as creation of larger breaks increasing its association with retinal detachment.

4. Trophic Retinal Holes

These are degenerative lesions not associated to vitreous traction. By histopathology there is a progressive loss of neurosensorial retinal layers creating a full thickness defect, often surrounded by pigment clusters. Retinal holes can appear anywhere in the retina, but are found more often between the equator and retinal periphery.

They have been described as occurring more frequently in highly myopic patients but have also been found in emetropic eyes.

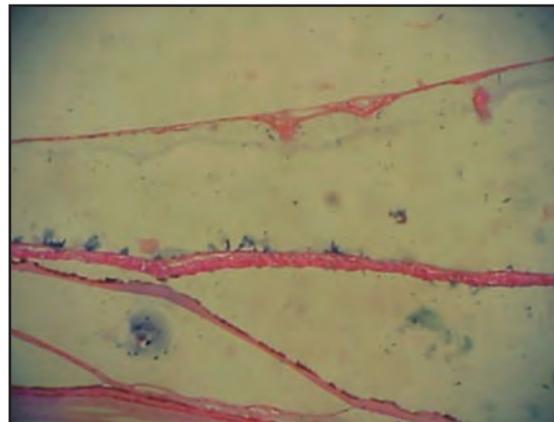


Figure 2: Retinoschisis 10X (Courtesy: Dr. Oliver Schneider).

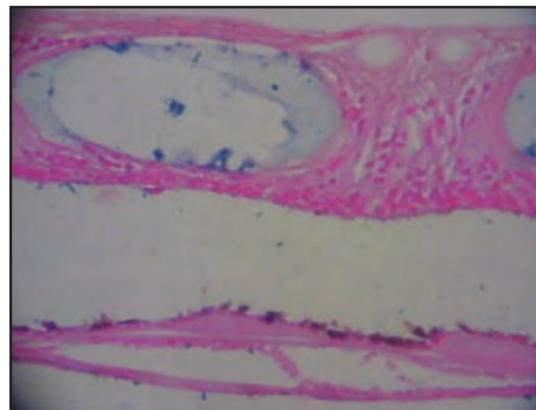


Figure 3:(Courtesy: Dr. Oliver Schneider).



Treatment of these lesions is rarely necessary unless vitreoretinal traction exists nearby or they are discovered within areas of lattice or detached retina.

5. Retinal Tears

Retinal tears are the result of vitreous traction located in abnormal sites of vitreous attachments during acute posterior vitreous detachment; such as paravascular unions, peripheral degenerative lesions or chorioretinal scars. It has been described that approximately 15% of all acute symptomatic posterior vitreous detachments have an associated tear¹⁸ (Figure 4).

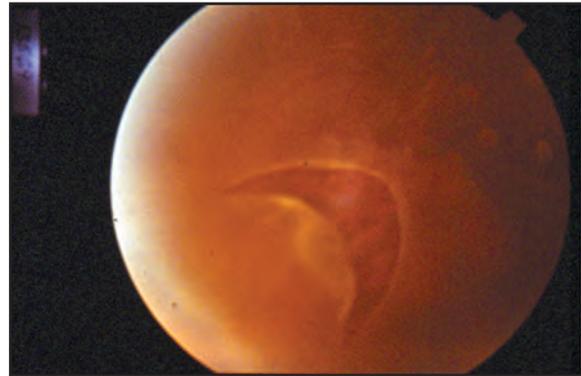


Figure 4: Horseshoe tear.

Table 2

NOT PREDISPOSING LESIONS
Meridional folds and complexes
Ora serrata bays
Ora serrata pearls
Non cystic retinal tufts
Zonular traction tufts
Cystoid peripheral degeneration
Pavingstone degeneration (Fig. 5)
Pars plana Cysts.
White with pressure degeneration

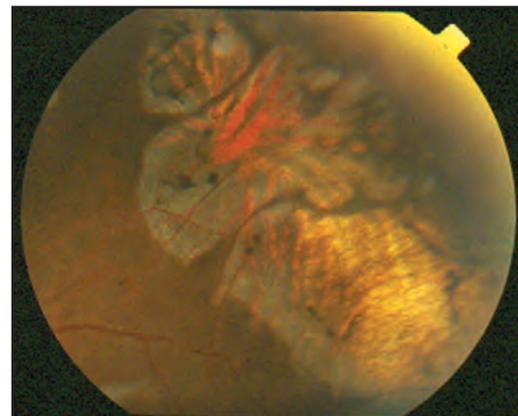


Figure 5: Pavingstone degeneration.



These lesions have different configurations: arrow head, horseshoe, L shape, H shape etc.

When the tear takes place over a vessel, vitreous hemorrhage can appear and has been reported that 70% of patients with vitreous hemorrhage associated to posterior vitreous detachment have tears. However, it may manifest just with photopsias and myodesopsias.¹⁸

The treatment of a recent, symptomatic retinal tear is not a matter of controversy, since these lesions are highly related to retinal detachment, prompt laser treatment is indicated.

6. *Dialysis*

This lesion is defined as a separation of the retina from its insertion at the ora serrata, they can be of either idiopathic or traumatic origin.

The first type occurs spontaneously, not associated to vitreous traction, located in the inferotemporal quadrant. Young males are more affected. Whenever a dialysis is found whether associated or not to retinal detachment it is mandatory to specifically search the other eye, since it is often bilateral.

Dialysis can cause a slowly progressive inferior retinal detachment, so laser treatment is indicated.

Dialysis of traumatic origin are preceded by direct contusion of the globe, the superonasal

quadrant is affected more often and can be associated to vitreous base avulsion. Since these are also related to retinal detachment, laser treatment is indicated.

INDICATIONS FOR LASER TREATMENT

The accurate selection of cases that can benefit from prophylactic laser treatment is still a matter of controversy; the decision must be based in all the factors we discussed previously.

There are retinal lesions that nobody would doubt in treating, such as a symptomatic superior retinal tear, meanwhile a small trophic pigmented asymptomatic retinal hole located inferiorly probably would not benefit from treatment. Between these two examples a great variety of lesions exist, and good clinical judgment and experience is required in order to avoid unnecessary treatment.

We must keep in mind that retinal detachment is infrequent, affecting 1 in 10,000 - 20,000 patients a year, while peripheral retinal degenerations can be found in 6 to 14% of the general population.^{4,20}

There are a lot of variables that must be taken into consideration before indicating treatment: Presence of symptoms, location of the lesion, type, size, presence of subretinal fluid, age, family history of retinal detachment, collateral eye condition, refractive error, life expectancy, occupation, associated conditions such as aphakia or pseudophakia.²⁰



The presence of symptoms such as entoptic phenomena is indicative of vitreoretinal traction, floaters are related to posterior vitreous detachment and also can be referred by patients with associated vitreous hemorrhage.

Superiorly located tears above the horizontal meridians are considered more dangerous, since they can produce rapidly progressive retinal detachments.

Tears found posteriorly are also dangerous since those are more in contact with intraocular currents if the vitreous is liquefied.

The presence of subretinal fluid surrounding a lesion makes us think of the need of prompt laser treatment.

Aphakia or pseudophakia combined with posterior capsule rupture increase the risk of retinal detachment.

As mentioned previously, lattice degeneration has firmly attached vitreous to its margins, so when acute posterior vitreous detachment takes place, tears can develop.

We must keep in mind that the objective of laser treatment is to create a barrier that blocks the transit of liquefied vitreous through a retinal break.

The chorioretinal scar generated by laser is not strong enough to avoid a retinal break formation during acute posterior vitreous detachment, thus it would not be useful to treat lattice degeneration if the vitreous is still attached, here the best behavior would be close observation.²³

Laser Photocoagulation

Among all different treatment methods to produce retinopexy (chorioretinal adherence) argon laser is the most popular.²² In the history of retinal detachment many methods have been used: diathermy, cryotherapy, xenon photocoagulation. But adverse effects such as epiretinal membranes and higher incidence of proliferative vitreoretinopathy have made argon laser a better technique¹⁹ (Table 3).

Table 3

ADVANTAGES OF ARGON LASER IN RETINOPEXY
SPARE HEMATORETINAL BARRIER
FASTER CHORIORETINAL ADHESION
LOWER INCIDENCE OF EPIRETINAL MEMBRANES

Argon green laser energy is completely absorbed by the retinal pigmentary epithelium and has little if no penetration to choroidal layers. It creates a gray-white burn by protein denaturalization involving internal and external retinal layers. Another advantage of this method is the great variety of application techniques; from the traditional method with a three mirror lens and slit lamp which allows easy visualization of the retinal periphery, the indirect ophthalmoscope with scleral indentation, to the laser probe used during vitrectomy surgery.

Different lasers have been used in prophylactic treatment of peripheral retinal lesions such as the Argon (514 nm), diode (810nm) and krypton (647nm) lasers (Table 4).

**Table 4**

TYPES OF LASERS	WAVE LENGHT
ARGON GREEN	514nm
DIODE	810nm
KRYPTON	647nm

Diode laser acts in the infrared, invisible specter and its absorption characteristics vary from argon laser. It penetrates deeper into the choroid, similar to the krypton, requires more energy in order to create a similar scar, and is more painful. Nevertheless it has been reported as efficient as argon laser. It has also been speculated that when creating deeper burns the chorioretinal adherence generated is more effective than with argon, but also increases the risk of Bruchs membrane rupture and choroidal hemorrhage.²⁴

Therefore argon laser is the preferred method when applying laser treatment.

Techniques for Laser Application

Once we have decided to treat a lesion and explained the patient the technique, the pupil should be widely dilated, with the patient sitting in front of the slit lamp and with a three mirror lens, the lesion must be located. In order to begin with light gray burns power is adjusted in approximately 200mw and with exposure time of 0.5 seconds. Size can vary between 200-500 microns. These parameters can be increased gradually until gray-white burns are obtained.

Densely pigmented eyes require less intensity in order to achieve an effective chorioretinal scar compared to less pigmented eyes. Nuclear sclerosis of the lens, vitreous hemorrhage or pigment can interfere with laser treatment.

Lesions must be surrounded with contiguous burns starting from the margins and placing 3 or 4 lines, avoiding treatment of choroidal tissue (Figure 6A-B).

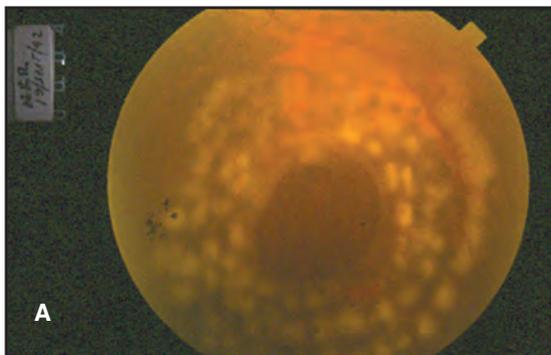
If the decision of prophylactic treatment of a lattice degeneration has been taken, not only the break within is treated, the margins of the lesion (lattice) should be completely surrounded.

When the lesion is located in the periphery and the anterior border is hard to reach, scleral indentation can be helpful, sometimes it might be necessary to consider a different method such as cryotherapy. This method could also be considered in cases of opaque media (Table 5).

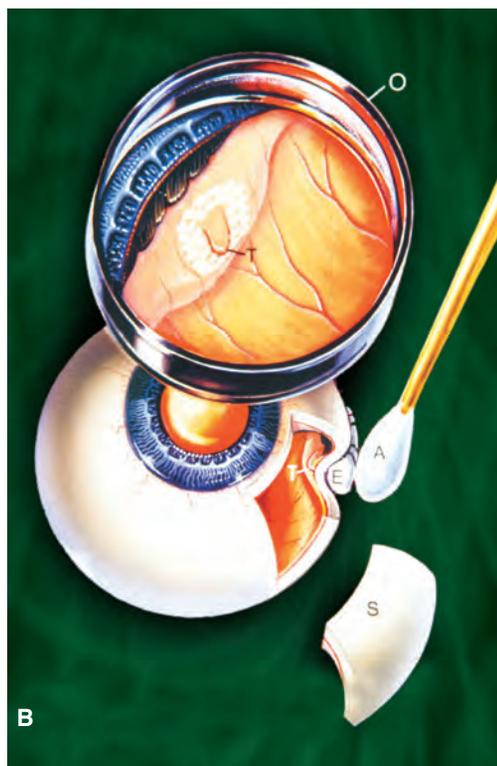
Complications

Laser treatment as a retinopexy method has only a few complications compared to cryotherapy, xenon photocoagulation or diathermy.

Epiretinal membrane formation has been reported with excessive treatment. When using small diameter laser burns (100-200 microns) accidental rupture of retinal vessels can happen.



A



B

Figure 6: A) Retinal tear already treated with laser. B) Final View of Buckle with Retinal Indentation and Laser Sealing. This internal/external conceptual illustration shows a cross section and corresponding surgeon's view of the final configuration of a circumferentially placed sponge explant (E). The cross section shows a portion of sclera (S) removed for clarity. The surgeon's view is through the indirect ophthalmoscope (O). Note the indented configuration in both views. The retina is reattached and the tear (T) is flat. Also note that the tear is properly positioned on the anterior slope of the invagination. (B: Art from Jaypee-Highlights Medical Publishers).

Table 5

ARGON LASER PARAMETERS FOR TREATMENT OF PERIPHERAL LESIONS	
POWER	Initially low, 100 a 200 mw until gray-white scar.
SIZE	200 a 500 microns.
EXPOSURE TIME	Beginning with 0.2 sec and increase according to burn.

Follow up is crucial, one week after treatment we can get a good scar. Sometimes a big tear can develop a retinal detachment despite laser treatment, presenting a subclinical retinal detachment which will require more aggressive treatment.

Complications are unusual and only a few trials with good follow up exist but these report high effectiveness, close to 100%.²⁵

The Role of Laser Treatment in Peripheral Lesions Predisposing to Retinal Detachment

We must keep in mind that the role of laser treatment in this type of lesions is to create a scar surrounding its margins, not mainly to increase chorioretinal adhesion, but to block the flow of liquefied vitreous to the subretinal space; thus the protective role of treating lattice or tufts does not really exist, because when a break from acute posterior vitreous detachment is generated even if previously treated it can pull and elevate the retina despite laser burns.

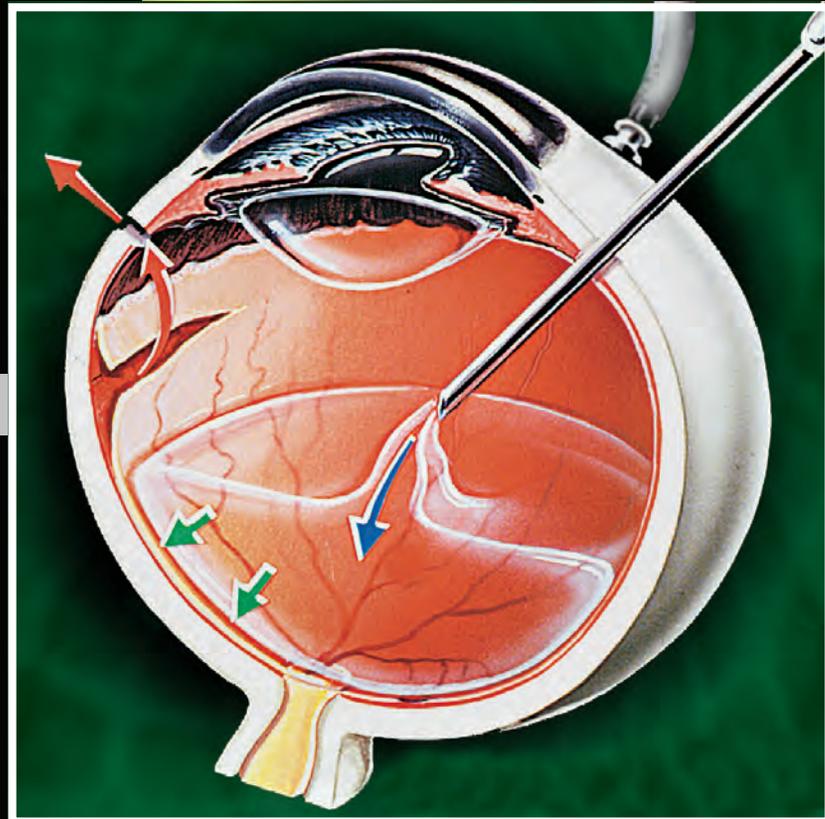
Careful evaluation of each patient is needed, and every fact must be taken into consideration before indicating prophylactic



laser treatment. Laser is a useful tool and should be used prudently. Photocoagulation is clearly indicated in retinal tears with persistent vitreous traction upon flaps of the tears. For most other entities, evidence of important value is still lacking. The best evidence-based recommendations for prophylactic therapy are contained in an American Academy of Ophthalmology publication.²⁶

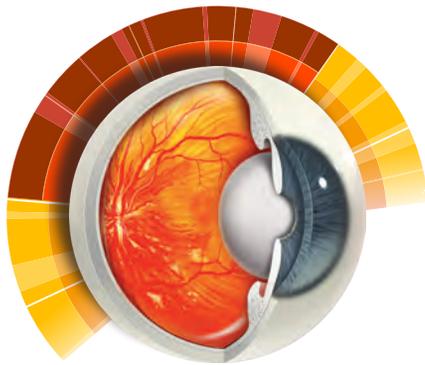
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Section 3

Essential Elements in Vitreoretinal Surgery



9

Indications of Intraocular Gases in Retinal Surgery

GHOLAM PEYMAN, MD.,
DARIUS MOSHFEGHI, MD

Introduction

Intraocular gas is a useful adjunct in the management of a wide variety of disorders of the posterior segment. Gases have been used advantageously for the outpatient management of retinal detachment (pneumatic retinopexy) as well as an invaluable intraoperative tool during vitreous surgery, macular hole repair,¹⁻³ and the management of complicated retinal detachment. Intraoperatively, gases have been used to manipulate the retina mechanically, to flatten retinal detachments and displace subretinal fluid, to maintain a clear view of the retina by displacing vitreous hemorrhage, and to maintain ocular tone. The function of the gas bubble postoperatively is to provide temporary internal tamponade of retinal breaks until a permanent chorioretinal adhesion occurs.

Innovations in the development and application of longer-acting gases in the last 25 years have provided a greater understanding of the clinical behavior of intraocular

gases in vitreous surgery. In this chapter we will summarize the current state of the art and review the indications, technique, and complications of intraocular gases in ophthalmic surgery. Emphasis is given to the characteristics of the gases most commonly used in vitreoretinal surgery.

History

Ohm is credited with the first injection of an intraocular gas (air) in 1911 to repair a retinal detachment,⁴ although the significance of closing retinal breaks in achieving reattachment was not known until Gonin's later discovery.^{5,6} It was Rosengren, however, who synthesized these concepts and advocated the use of intraocular air in conjunction with diathermy and drainage of subretinal fluid to create permanent retinal apposition to the retinal pigment epithelium (RPE).⁷⁻⁹ Rosengren's success was soon overshadowed by the innovation and success of scleral buckling in the mid-20th century.¹⁰



Work by Norton^{11,12} and others¹³⁻¹⁸ popularized the intraocular use of sulfur hexafluoride (SF_6) gas for internal tamponade of retinal breaks. Gases with longer duration and greater expansile properties—the perfluorocarbon family of gases—were first investigated by Vygantas¹⁹ et al in 1973 and came into greater clinical use in the early 1980's.²⁰⁻²⁸

Pneumatic retinopexy was introduced by Domínguez²⁹ in Spain and popularized by Hilton and Grizzard.³⁰ This technique, unlike the conventional repair of retinal detachment, could be performed in the outpatient setting without surgical buckling techniques (Figure 1). The advantages and limitations of this alternative treatment modality are beyond the scope of this chapter but are reviewed in several excellent works.²⁹⁻³²

Bubble Dynamics

An expansile concentration of gas injected intraocularly undergoes three phases: bubble expansion, equilibration, and bubble dissolution. Certain environmental factors and specific gas characteristics govern the behavior of the gas bubble through these stages.

The first stage of gas transfer occurs after a pure gas is injected into the vitreous cavity. Rapid bubble expansion commences as host tissue gases (oxygen, carbon dioxide, and water vapor) diffuse into the bubble along partial pressure gradients.^{10,33-35} Nitrogen enters the bubble more slowly than oxygen and carbon dioxide. Continued bubble expansion is halted (maximal expansion is achieved) when the

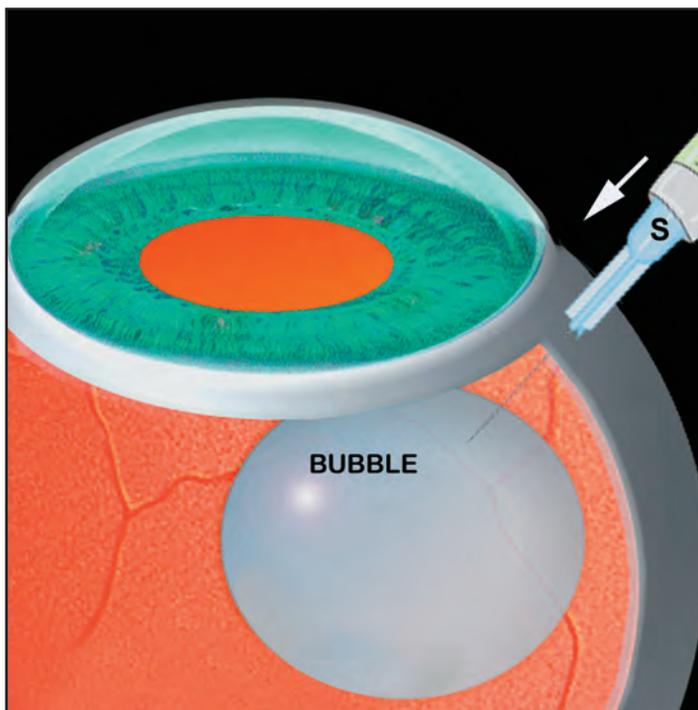


Figure 1: Pneumatic Retinopexy - Intraocular Bubble Injection. This technique, unlike the conventional repair of retinal detachment, could be performed in the outpatient setting without surgical buckling techniques. Most commonly intraocular gases used such as SF_6 or C_3F_8 are injected through a small 27 gauge needle (S). (Art from Jaypee Highlights Medical Publications).



rate of pure gas diffusion out of the bubble is equal to the rate of nitrogen diffusion into the bubble. Principal factors contributing to a slow rate of diffusion include a low coefficient of diffusion, poor water solubility, and a high molecular weight.^{10,17} Although the time required to achieve maximal expansion varies among specific gases, the most rapid rate of initial bubble expansion is fairly constant despite the type of expansile gas used and typically occurs in the first 6 to 8 hours.¹⁰ Vitreous convection currents are thought to play a major role during this time period, although this theory is based on *in vitro* studies.³⁴

The second stage—nitrogen equilibration—occurs as the partial pressures of nitrogen within the gas bubble and in the surrounding tissue equilibrate.^{17,35} At the beginning of this phase, the bubble has achieved maximal expansion, but soon loses volume as pure gas leaves the bubble (because of a high pressure gradient) at a rate greater than that at which nitrogen enters it (as a result of a decreasing partial pressure gradient).^{17,34,35}

The third stage is slow, predictable reabsorption. The concentration of various gases within the bubble remains constant throughout bubble dissolution that follows first-order exponential decay.²⁸ Although gas bubbles may remain in the eye for periods of several days to several weeks (depending on the specific gas injected), the actual therapeutic effect of such bubbles is of much shorter duration. Thompson reported that the maximal effective duration of tamponade is equal to the passage of three half-lives.³⁶

Chang noted that a 50% gas bubble volume is desirable to achieve effective tamponade of most retinal breaks; however, this therapeutic volume of gas is only present in the eye for approximately 25% of the actual duration of gas in the eye.¹⁰

The possible effects of the presence or absence of vitreous and/or the crystalline lens on the intraocular longevity of gas are still controversial. Wong and Thompson demonstrated that the phakic, non-vitreotomized eye maintains perfluoropropane (C_3F_8) and SF_6 significantly longer than the aphakic, vitreotomized eye.³⁷ Citing possible errors in methodology, Lincoff disputed the findings of Wong and Thompson which contradicted his prior study²⁸ and he presented new data to support this claim.³⁸

Clinical and Physical Properties of Specific Gases

Various gases have been used for intraocular injection (Table 1), each with varying properties that make them desirable for a specific clinical situation. Gases may be classified by their chemical structure, behavior (expansile or non-expansile), and *in vivo* longevity (short-acting, intermediate-acting, and long-acting). The ideal gas is clear, colorless, nontoxic, and inert; maintains a high aqueous-gas interface surface tension; and remains in the eye sufficiently long to effect permanent chorioretinal adhesion.³⁹ The three most commonly used gases in vitreoretinal surgery: air, SF_6 , and C_3F_8 (Table 2) are discussed.



Table 1 Behavior of pure gases for intraocular injection	
Nonexpansile Gases	Expansile Gases
*Air Argon (Ar) Carbon dioxide (CO ₂) Helium (He) Krypton (Kr) Nitrogen (N ₂) Oxygen (O ₂)	<u>Nonperfluorocarbon gases</u> Sulfur hexafluoride (SF ₆)
*Air is not a pure gas	<u>Perfluorocarbon gases</u> Perfluoromethane (CF ₄) Perfluoroethane (C ₂ F ₆) Perfluoropropane (C ₃ F ₈) Perfluoro-n-butane (C ₄ F ₁₀)

Table 2 Properties of air, SF ₆ and C ₃ F ₈ in vivo			
Gas	Expansion Multiple	Intraocular Longevity	Nonexpansile Concentration (%)
Air	0	2-4	—
SF ₆	1.9-2.2	10-14	18
C ₃ F ₈	4	55-65	14-16



Air

Air was the first gas used in vitreoretinal procedures.^{4,7-9} Air has a role as an intraoperative tool:

- 1) Improve visualization during intravitreal surgery by displacement and hemostasis of vitreous hemorrhage.
- 2) Maintain the intraocular volume after drainage of subretinal fluid in scleral buckling surgery.
- 3) Perform a mechanical unrolling of large tears and flattening of fishmouth tears that result from retinal folds (although the perfluorocarbon liquids lend themselves more readily to this function).
- 4) Tamponade suspected but undetected retinal tears (in cases in which the retina fails to reattach) in the immediate postoperative period.
- 5) Provide retinal tamponade in cases of rhegmatogenous retinal detachment.^{10,36,40} Air remains in the eye for 1 to 2 days and does not expand under normal conditions.

Sulfur Hexafluoride (SF₆)

SF₆ was one of the earliest gases to be used for intraocular injection and is still widely used.⁴¹ Sulfur hexafluoride was chosen as an alternative to air when it was shown that this inert gas provided longer, more effective tamponade of retinal tears and detachments than air and was relatively free of harmful side effects.^{15,16,18} One milliliter of pure SF₆ gas expands to approximately twice its original

size, attains maximal expansion two days after injection, and remains in the eye for 10-14 days. At a concentration of less than 20%, SF₆ loses its expansile property.⁴²

Perfluoropropane (C₃F₈)

The use of C₃F₈ has become routine in the management of complicated retinal detachment.⁴¹ Since its introduction by Lincoff in the early 1980s, C₃F₈ has been an attractive vitreous substitute in retinal detachment surgery because its prolonged intraocular duration (55-65 days) allows effective chorioretinal tamponade to occur.^{22,23} C₃F₈ remains in the eye four times longer than SF₆ while exhibiting a side-effect profile similar to that of SF₆.²³ A C₃F₈ bubble expands to four times its original volume 72 hours after injection.²² C₃F₈ becomes non-expansile at a concentration of less than 12%⁴² and appears to be slightly more toxic than SF₆.

Clinical Estimation of Gas Volume

Most clinicians describe gas fills as a percentage of the vitreous cavity based upon indirect ophthalmoscopy. For example, a 50% bubble describes a bubble whose inferior meniscus approaches the level of the fovea, whereas a 20% bubble would have as its inferior meniscus the level of the superior limbus. To avoid parallax error, it is imperative that the examiner's eyes are at the same height as the patient's eyes and that the patient and examiner are sitting perfectly upright.³⁷



Choice of Gas Based Upon Clinical Situation

The surgeon must choose the proper gas, concentration, and volume to be injected. The primary role of the gas bubble is to provide internal tamponade of retinal breaks long enough for a permanent chorioretinal adhesion to form. The buoyant nature of gases not only provides internal tamponade, but this gas-fluid interface also serves to block the break and prevent fluid from entering the subretinal space.

To achieve these goals, the surgeon must choose a gas that will remain in the eye sufficiently long to perform these tasks. Superior breaks usually require smaller volumes of gas compared to inferiorly or posteriorly located lesions. Posterior and inferior breaks require larger bubbles and proper patient positioning for effective tamponade. A 50% bubble in the eye of a patient maintaining prone positioning is generally sufficient to treat posterior lesions effectively. Smaller bubbles (between 20-50%) are needed for treatment of macular holes with the patient prone.³⁶ Lesser volumes can also be used for the treatment of superior breaks with the patient assuming upright positioning.³⁶

Increased intraocular longevity—dictated by gas type and concentration—is required in the treatment of multiple or complicated breaks. Air is often injected intraoperatively during scleral buckling procedures after drainage of subretinal fluid to maintain ocular tone and is chosen because it will be rapidly absorbed into the blood stream after

serving its temporary support function. By contrast, perfluoropropane is more appropriate for treating multiple breaks complicated by residual vitreous traction in which prolonged tamponade is required. Several studies have attempted to outline decay rates of specific gases at varying concentrations in a variety of clinical conditions.^{23,28,38,42,43}

Intraocular Pressure

As Thompson noted, scleral rigidity does not permit expansion of the eye after intraocular injection of gas.³⁶ Therefore, an acute rise in intraocular pressure (IOP) is seen in approximately 36% of eyes after vitreous surgery;⁴⁴ however, unlike some eyes injected with silicone oil, those injected with long-acting gases rarely succumb to chronic IOP elevations.⁴⁵ This phenomenon occurs for several reasons. Although the mechanical effect of the gas bubble against the iris-ciliary body process may result in angle-closure glaucoma, this is actually one of the less common mechanisms. More frequently, an acute rise in IOP within the first 48 hours of surgery occurs as a result of the rapid expansion of the bubble, decreased aqueous outflow caused by intraocular inflammation, or decreased uveoscleral outflow in cases in which an encircling band has been placed.^{44,46} The rise in IOP as a result of intraocular gas injection can be difficult to differentiate from a similar rise caused by a steroid response. The distinction is typically based upon the fact that the former occurs in the early post-operative period while the latter becomes a problem later in the recovery period.



Because the Tono-Pen tonometer is known to underestimate IOP in gas-filled eyes,^{47,48} the surgeon should be mindful of established conversions⁴⁸ or utilize more reliable methods such as Goldmann applanation tonometry.

The eye compensates for increased IOP by correspondingly increasing aqueous outflow; however, this mechanism often cannot overcome the large increases in IOP encountered in the early postoperative period. Management of the acute rise of IOP after vitreous surgery with long-acting gases typically involves topical or systemic carbonic anhydrase inhibitors. Anterior chamber paracentesis may provide

temporary relief of elevated pressure and, rarely, aspiration of previously injected gas may be required (Figure 2). The complication of central retinal artery occlusion must be considered after injection of an expansile concentration without removal of vitreous, as in pneumatic retinopathy. Frequent monitoring of the fundus in the first 6 to 8 hours after surgery is warranted in such cases.

Prior to intraocular injection of an expansile gas, gonioscopy should be performed to detect eyes with compromised angles, which may have areas of closure caused by peripheral anterior synechiae or neovascularization. Only

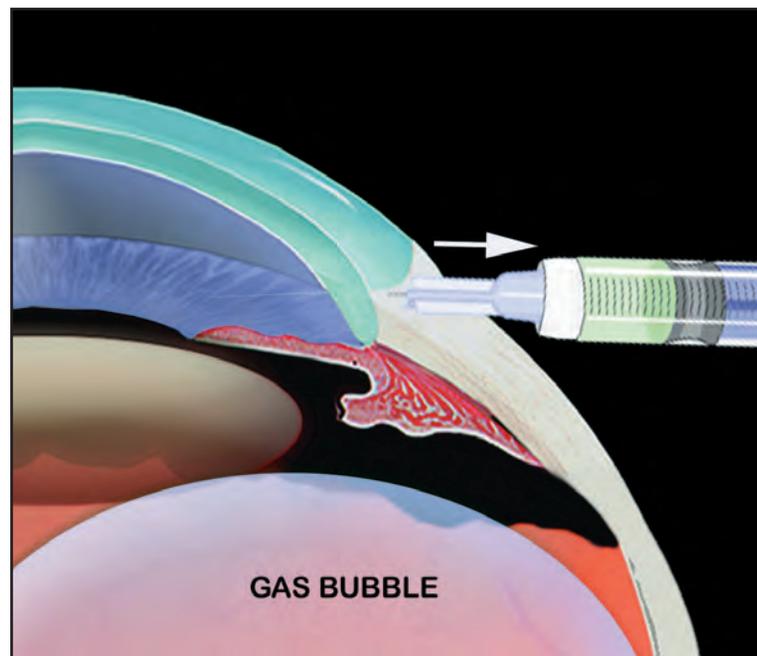


Figure 2: Anterior Chamber Paracentesis. This procedure may provide temporary relief of elevated pressure after injection of intraocular gas. Aspiration of previously injected gas may be required. The complication of central retinal artery occlusion must be considered after injection of an expansile concentration without removal of vitreous, as in pneumatic retinopathy. 27 gauge needle. (Art from Jaypee Highlights Medical Publications).



non-expansile gases should be used in these eyes, and all patients with a significant gas fill should be advised to assume a face-down position to avoid aphakic pupillary-block glaucoma, angle-closure glaucoma, and lenticular opacities.²¹

Effect of Gas on Ocular Structures

In addition to rises in IOP, intraocular gases can have a variety of adverse effects on the ocular structures. Chief among these are crystalline lens and capsular opacities, intraocular inflammation, vitreous changes, corneal endothelial damage, proliferative vitreoretinopathy (PVR), and macular pucker.⁴⁹ Other complications include injection⁵⁰ or subsequent migration of subretinal gas, creation of new retinal tears, anterior dislocation of an intraocular lens implant, and the rare possibility of endophthalmitis.

Lens opacities and corneal endothelial damage are thought to be caused by the mechanical effect of the bubble against these structures, not as a result of its chemical composition. The presence of the gas bubble is believed to interfere mechanically with the normal metabolism of these structures. Therefore, face-down positioning by the patient can alleviate the mechanical irritation of the gas bubble to the lenticular surface or the corneal endothelium in an aphakic eye. Most cases of keratopathy resolve over days to weeks,

but corneal decompensation is a real concern in an unfortunate subset of patients.

Recent studies on the rabbit retina suggest that retinal tamponade with long-acting gases results in histopathologic changes in the superior retina (thinning or disappearance of the outer plexiform layer and abnormally increased glutamate distribution).⁴⁹ Further studies are needed to determine if these ill-effects are seen in the human retina as a result of prolonged tamponade by supposedly inert chemical gases.

Storage

Intraocular gases are typically maintained in the manufacturer's cylinder. Gas is dispensed from the cylinder via a two-filter system to guard against microbiologic or particle contamination. One syringe is used to collect the gas from the "dead-space" of the apparatus and is flushed several times before the second syringe is put in place and filled with pure gas. A 22- μm filter removes most particulate and microbiologic contaminants and should be used when filling syringes with either gas from the manufacturer's cylinder or when collecting air from the operating room environment or outpatient setting.⁵¹ While temporary storage of gas in vacuum-sealed containers or in capped syringes for use in remote areas has been described, the practitioner should note that the concentration of the gas in these make-shift storage units varies considerably, especially with the passage of time.^{52,53}



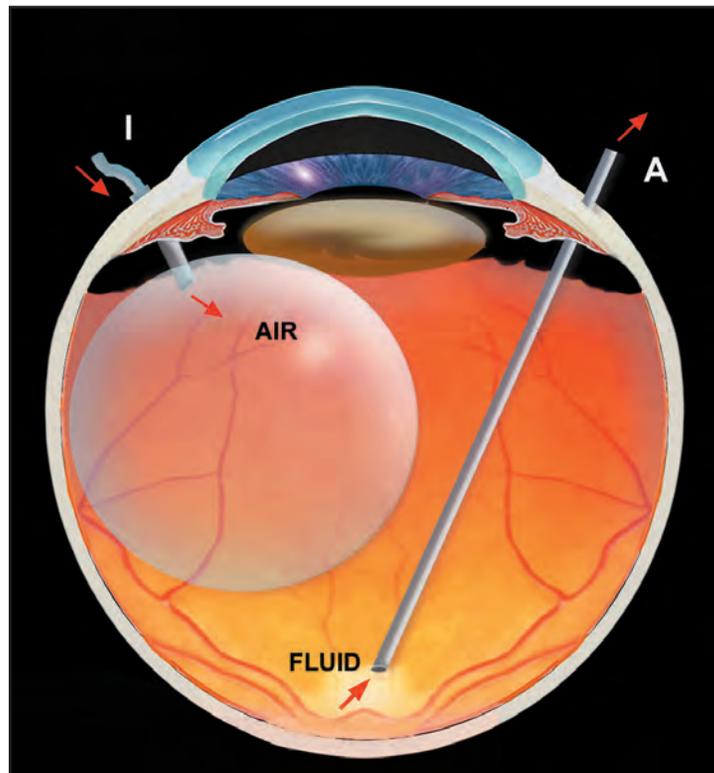
Air-Fluid Exchange in an Operating Room Setting

Air or gas is used intraoperatively after vitrectomy. Air enters the eye through an infusion cannula (Figure 3), which is connected to the air pump of the vitrectomy system. Generally, the infusion line for irrigation solution and air tubes are connected by a three-way stopcock to the infusion cannula sutured at the pars plana site. Peyman developed an illuminated switch on the air pump that indicates whether the air or infusion fluid line is open.⁵⁴ Because the system is independent from the room illumination,

the operating room nurse can activate the air or the infusion fluid line by pressing the switch without disturbing the dark adaptation of the surgeon. In the absence of this system, the surgeon must always be cognizant of the status of the infusion line (air, fluid, or off).

Air-exchange can be combined with internal drainage of subretinal fluid (Figure 4).⁵⁴ The air pump pressure is set at approximately 50 mm Hg. The air pump maintains the IOP automatically by increasing the flow of the air inside the eye to offset leakage of any air through the sclerotomies. Air enters the eye through the infusion cannula while

Figure 3: Air-Fluid Exchange Through a Flute or an Extrusion Needle (A). Infusion Cannula (I). (Art from Jaypee Highlights Medical Publications).



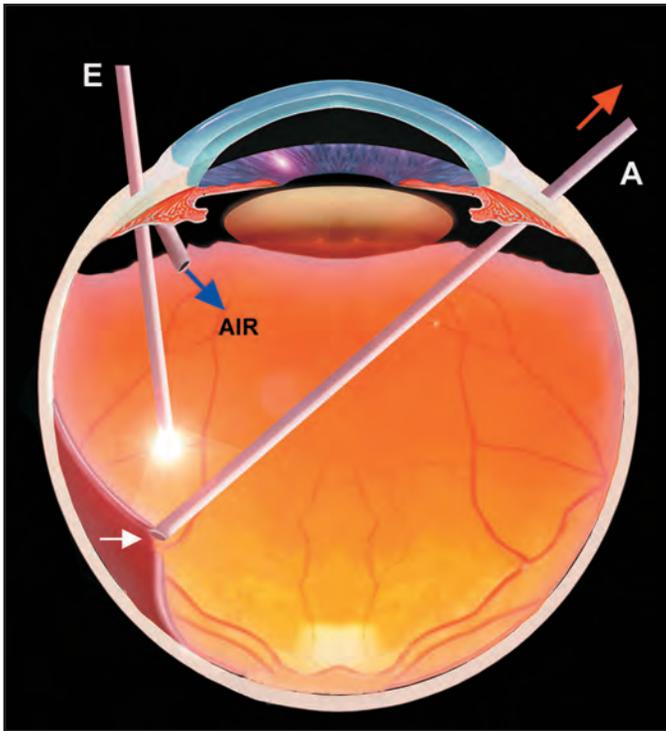


Figure 4: Air-Fluid Exchange and Internal Drainage of Sub-retinal Fluid (white arrow) with the Extrusion Needle (A). Endoilluminator (E). (Art from Jaypee Highlights Medical Publications).

aspiration of fluid in the anterior vitreous cavity is performed with either a fluted needle or extrusion handpiece. The blunt or tapered needle, called an extrusion handpiece, is usually connected by a polyethylene tube to the vitrectomy console, which provides vacuum. The needle is vented externally through an opening on the body of the instrument similar to some disposable vitreous suction cutter handpieces. Aspiration of fluid vitreous or subretinal fluid is performed when suction is applied to the tube and the operator's index finger is used to close the aperture on the body of the instrument. When the aperture is opened, air is sucked into the system,

and the suction becomes discontinuous. If the suction line is completely clamped, the suction needle functions like a flute needle. In such a situation, the IOP forces the fluid from the vitreous cavity through the needle and out of the opening on the handle of the instrument.⁵⁵

Initially, multiple bubbles enter the eye, coalescing into one bubble almost immediately. The needle is then gradually moved toward the posterior pole when a posterior retinal tear is present or toward a prepared retinotomy site. Subretinal fluid is pushed posteriorly as the air-fluid exchange progresses⁵⁶ and is evacuated using a flute needle.⁵⁷



Drainage of subretinal fluid through a retinotomy can be performed with an extrusion cannula, which is blunt tipped, tapered, or has a soft silicone tip or extension.⁵⁸ The cannula, attached to an automated suction, is placed slightly anterior to the retinal hole until the subretinal fluid is almost completely removed. At this point, a meniscus of fluid is touched by the cannula. This maneuver is repeated until reattachment of the retina has occurred. When the fluid falls below the level of the cannula tip, a bright reflex is observed as the needle touches the fluid, which helps avoid direct contact between the needle tip and RPE. The positive pressure created by the infusion of gas and controlled linear suction applied to the cannula results in the removal of subretinal fluid via the suction needle.⁵⁶

The retina must be carefully observed during the air-fluid exchange and the internal drainage of subretinal fluid. When areas of epiretinal traction exist, forceful air injection may cause existing tears to enlarge or may create large tears at the site of preexisting traction. Failure of the retina to flatten or the presence of subretinal air indicates residual traction that must be relieved before the retina will reattach. Subretinal air can migrate anteriorly and may not easily be removed. During air-fluid exchange, residual areas of traction become identifiable. Subsequent visualization of the retina after gas-fluid exchange requires a corresponding change in the viewing lens because of the difference in refractive indices between fluid and gas.

Air-Fluid Exchange in an Outpatient Setting

Air-fluid exchange in an outpatient setting following vitrectomy is indicated for recurrent vitreous hemorrhage, to remove intravitreal blood. This procedure facilitates retinal examination, allows management of possible complications, prevents unnecessary delay in visual recovery, and may protect against re-bleeding in some instances.

Stern and Blumenkranz⁵⁹ recommend the use of a 20% mixture of SF₆ and air. Two milliliters of pure SF₆ are placed in a 10-mL syringe. Sterile tubing, connections, and a 0.22- μ m Millipore filter are attached to the gas tank to ensure sterility; 8 mL of air is withdrawn into the syringe to provide the desired concentration of gas. Gas is then expelled from the syringe until 5 mL remains. The patient is placed in a prone position in bed with the chin supported by a pillow. Following topical anesthesia, a wire lid speculum is placed in the patient's eye. Using light from either an indirect ophthalmoscope or a flashlight held by an assistant, the surgeon stabilizes the eye with a cotton-tipped applicator, and air-fluid exchange is done through the limbus in aphakic patients.

We have found that patient stability and surgical control are achieved by using the slit-lamp chin rest to support the head. The slit-lamp light beam is used to illuminate the eye. Two acetaminophen tablets are given

30 minutes before the procedure to reduce or eliminate ocular discomfort. After the application of topical anesthesia and prior to the procedure, the cul-de-sac is irrigated first with a 10% povidone-iodine solution and then with sterile balanced saline solution. A drop of topical gentamicin is placed on the cornea, and the eye is entered through the temporal limbus with a 27-gauge, needle attached to the syringe. Before it enters the eye, the needle track is beveled to prevent escape of intraocular gas and the production of hypotony when the needle is withdrawn from the eye (Figure 5).

The needle is placed slightly below the pupil, fluid is withdrawn, and gas is injected in 0.3 mL increments. Wide variations of IOP must be avoided to prevent severe ocular pain. Fluid collects in the bottom of the syringe. When the anterior chamber begins to fill with gas, the needle is moved inferiorly, and additional fluid is withdrawn and replaced with air. When the eye has been filled with gas, the needle is withdrawn. If hypotony is present at the end of the procedure, the IOP is re-established by injecting a 20% mixture of SF₆ and air through the limbus with a 30-gauge, 0.5-inch needle in aphakic patients. The same procedure is performed through the pars plana in phakic eyes.

Retrobulbar anesthesia is used to perform this procedure in phakic eyes. The patient is placed in a prone position in bed, with the head tilted toward the side of the involved eye. Following insertion of the lid speculum, the

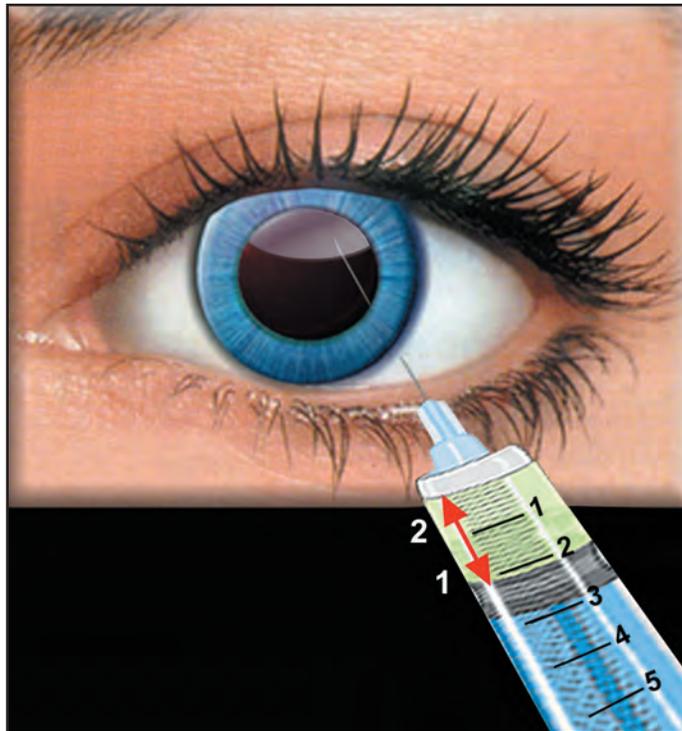


Figure 5: Schematic Representation of Gas-Fluid Exchange through the Limbus. Arrow indicates back-and-forth motion of the 5cc syringe piston for withdrawal of fluid and injection of gas. (Art from Jaypee Highlights Medical Publications).

needle is inserted through the temporal pars plana 4 mm behind the limbus in a shelved (self-sealing) fashion. When the needle is visualized behind the lens, the exchange is started. The needle is gradually retracted as gas accumulates in the vitreous cavity. The procedure is terminated when the vitreous cavity is filled with air, which begins to enter the syringe. Following the procedure, IOP is measured by applanation tonometry. A drop of gentamicin is placed on the eye and the



IOP is recorded 4 to 6 hours later and again the following morning.⁵⁹

Positioning of the patient may vary during this procedure.^{60,61} The patient may be placed in a face-down position in bed or on a stretcher with the head resting on the arms, which are folded across a pillow.

In order to avoid the phenomenon of “fish eggs,” the needle is positioned so that its tip is inside the gas bubble before injection continues. This causes the bubble to enlarge with additional gas but is only applicable when two needles are used, one for injection of gas and the other for withdrawal of fluid. Careless maneuvering of the needle to place the tip within the preexisting bubble may result in inadvertent contact between the needle and lens with subsequent cataract formation.⁶⁰

After the needle has been withdrawn, we usually apply a cotton swab with gentamicin ointment to the needle tract to prevent the escape of intraocular gas. Topical gentamicin drops are applied after the procedure is finished. Replacement of a needle prematurely withdrawn before completion of the procedure should be done through a separate site because insertion through the initial tract may stretch this opening and result in subsequent leaks.⁶⁰ When iris becomes incarcerated in the inner corneal wound, gentle massage with a blunt instrument over the external cornea in the area of the incarceration usually releases the tissue.⁶² When removing blood, a 30-gauge needle may become obstructed; a 25-gauge needle creates too large a tract in the cornea, which may subsequently leak; utilization of a 27-gauge needle may be preferable.⁶²

Nitrous Oxide Anesthesia

The use of nitrous oxide (N_2O) should be discontinued within 20 minutes of intraocular injection of a gas bubble to allow depletion of N_2O in significant concentrations from the periocular tissues.^{63,64} N_2O is extremely soluble in the bloodstream, allowing rapid diffusion of the gas into the bubble resulting in dramatically increased IOP in the immediate postoperative period. After N_2O anesthesia is stopped, the N_2O collected in the intraocular gas bubble then diffuses back into the bloodstream, leading to subsequent hypotony.

Flying and Intraocular Gases

The majority of aircraft decompress cabin pressure to less than 8000 feet after reaching cruising altitude in an average of 27 minutes.²⁸ A 10% gas bubble can be safely tolerated through a decompression to 8000 feet above sea level.²⁷ Larger gas bubbles are tolerable at lower altitudes.⁶⁵ Pre-flight medication with topical glaucoma agents has not been found to be helpful and can result in choroidal effusion after the plane returns to sea level. Prudence dictates that the patient be properly informed of the risks of flying before surgery is performed and that flying be avoided in the presence of significant residual bubble.

Similar precautions must be taken prior to SCUBA (self-contained underwater breathing apparatus) diving (or hyperbaric oxygen therapy). As Thompson noted, although the eye may become hypotonic during the dive, it is the rapid ascent to the surface that can result in very elevated IOP.³⁶



Conclusions

Intraocular gases are extremely versatile and powerful tools for the vitreoretinal surgeon. Gases are able to plug retinal holes, provide internal tamponade for retinal breaks to create a firm chorioretinal adhesion, and are an invaluable intraoperative device for maintenance of the geometry of the globe and to facilitate visualization and manipulation of the retina. Each gas has unique characteristics which makes it useful for specific clinical situations. Clearly a thorough understanding of the properties and applications of these gases is needed to make an informed clinical decision regarding their use.

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10

Application of Perfluorocarbon Liquids in Vitreoretinal Surgery

STANLEY CHANG, MD

Perfluorocarbon liquid (PFCL) is colourless and odourless, and has a high specific gravity and low viscosity.

First used extensively during World War II (the Manhattan Project) as handling agents for the uranium that was to become the world's first atomic bomb, then as an artificial blood substitute, and finally as a sophisticated surgical tool in the management of complex retinal disorders, the physical and chemical properties of perfluorocarbon liquids have fascinated and aided the worlds of science and medicine for over 40 years.

The intraoperative use of PFCL in vitreoretinal surgery was introduced in 1987 by the author for the treatment of giant retinal tears, retinal detachments with proliferative vitreoretinopathy (PVR), and traumatic retinal detachments.¹⁻⁶ PFCL has also been used to reposition dislocated crystalline lenses and implanted intraocular lenses (IOLs).⁷⁻¹⁰ and when a subretinal haemorrhage is removed, for example during surgery for complicated age related macular degeneration.^{11,12}

CHEMICAL AND PHYSICAL PROPERTIES

Chemical Properties

Perfluorocarbons are fully fluorinated analogues of hydrocarbons. They form a special family of compounds whose chemical and physical properties can be most closely compared to those of inert gases. Their chemical formulas give us an indication as to their physical state. Those with 1 to 4 carbon atoms are gases. The straight-chain compounds (alkanes), C_6 to C_9 are liquids at room temperature, and most of the cyclic compounds in the C_6 to C_{10} range are liquids, but with increasing viscosities. Perfluorocarbon liquids are colorless, odorless, non-flammable, high specific gravity (1.6 to 2.1) materials, which are chemically and biologically inert when pure. They are stable to temperatures as high as 400 to 500° Celsius.



The term “fluorocarbon” is often incorrectly used in literature to describe chlorofluorocarbon refrigerant and propellant gases (CFC’s). These materials have heteroatoms, mainly other halogens, and differ from the perfluorocarbon compounds, which contain exclusively carbon and fluorine atoms. The environmental impact associated with CFC’s is not present in perfluorocarbons.

Various types of perfluorocarbon liquids have been manufactured for use as coolants, dielectric fluids, and test fluids in the manufacture and operation of electronic devices. These perfluorocarbons are not of sufficient purity to be chemically or biologically inert. Purified compounds such as perfluorodecalin, perfluorotripropylamine and perfluorooctyl

bromide have been used in biological/medical applications as synthetic oxygen carriers (blood substitutes), and as X-ray and NMR imaging agents, yet in the case of cyclic compounds such as perfluorooctyl bromide, they remain chemically active.

Over many years, stimulated by the work of the author, there has been a concerted worldwide effort to investigate the potential and utility of perfluorocarbon liquids as a surgical adjunct during vitreoretinal surgery. The interest is due to several of the unique physical and chemical properties of the compounds, and has centered primarily on perfluoro-n-octane, perfluorodecalin, perfluorophenanthrene and perfluorotriethylamine (Figure 1).



Figure 1: Essentials of Perfluorocarbon Liquids. Its high density and low viscosity allow perfluorocarbon liquids to provide a significant tamponade force that stabilizes the retina and gives the surgeon the ability to manipulate the retina with greater ease. (Art from Jaypee – Highlights Medical Publishers).



In January 1987 (Experimental Vitreous Replacement with Perfluorotributylamine, *Am. J Ophthalmology*. 103: 29-37) I described the ideal physical and chemical attributes of a perfluorocarbon liquid suitable for use in vitreoretinal surgery as 1) high specific gravity, 2) optically clear, 3) immiscible with water or blood or other common organic compounds, 4) low viscosity, 5) a high interfacial tension in saline, 6) high vapor pressure rate 7) a refractive index significantly different from aqueous and 8) a significant tamponading effect. Today, those parameters remain essential for the utility of perfluorocarbon liquids in vitreoretinal surgery.

Similarities in names of the various perfluorocarbon liquids have even contributed to some confusion encountered in discussions of the merits of the several compounds for use in vitreoretinal surgery. For instance, perfluoro-n-octane and perfluorooctane are often confused. Perfluoro-n-octane is composed of essentially pure (99.91%) straight chain octadecafluoro-n-octane, without isomeric impurities or fluoro-olefin impurities, as confirmed by gas chromatographic analysis. Perfluorooctane is produced as an industrial product, with several industrial applications. This is a material containing a large mixture of isomers such as C₆, C₇ and C₈ perfluorocarbons, and impurities such as ethers), and non-fully fluorinated structures.

In a published paper of perfluorocarbon heavy liquids, Robert Bourke and Peter Cooling point out that "although safe for intraoperative

use, most studies have shown that long-term tamponade (> 2 weeks) is associated with retinal changes that may be ascribed to two mechanisms – chemical toxicity or mechanical effects. Mechanical compression causes atrophic changes in dependent retina, whereas chemical toxicity is manifested as a macrophage and fibroblastic (PVR and epiretinal membrane) response."

Retinal changes include displacement of photoreceptor nuclei into the rod and cone layer (photoreceptor drop down), distortion of photoreceptor outer segments, narrowing of the outer plexiform layer, and ultimately retinal pigment epithelial hypertrophy. These changes are confined to the dependent retina. This probably represents a mechanical effect as analogous changes have been noted in the superior retina following prolonged retinal contact with silicone oil. Other findings that might be mechanical in origin include corneal endothelial damage and mild lens opacification following prolonged contact with perfluorocarbon liquids. This may again be equivalent to the effects of silicone oil, where a relatively inert substance blocks normal metabolic access to the lens or corneal endothelium.

ERG changes, including decreased b wave, a wave amplitude and increased latency, might be altered electrical conductivity rather than toxicity, since serial ERG's following removal of perfluorocarbon liquids, demonstrate recovery of the retinal function at one week after removal of the liquid.



Biologic intolerance manifests as preretinal membrane formation and vitreous infiltration consisting of foamy macrophages that contain ingested emulsified perfluorochemical. Pre-retinal fibrosis may ensue, and emulsification associated with macrophage ingestion may result in trabecular obstruction and subsequent elevation of intraocular pressure.

Fibroblasts may proliferate, contributing to epiretinal membrane formation and PVR.

When I introduced these high, specific gravity, low viscosity, immiscible, optically clear liquids to the world as an adjunct to the successful treatment of proliferative vitreoretinopathy and giant retinal tear(s), I demonstrated the value of these physical properties over those of previously existing retinal tamponade systems.

Physical Properties

High Specific Gravity

The most surgically significant physical characteristic of these heavy liquid compounds would certainly seem to be their high specific gravity. This property enables perfluorocarbon liquids to gently but uniformly flatten the detached retina by displacing subretinal fluid. As the perfluorocarbon is slowly introduced over the optic disc, its heavier-than-water specific gravity permits it to sink to the posterior retina immediately (Figure 2). As more material is added, the displaced subretinal fluids are forced anteriorly ahead of the meniscus of the perfluorocarbon liquid



Figure 2: Injecting Perfluorocarbon Liquids. After a total posterior vitrectomy, the surgeon injects the perfluorocarbon liquid very slowly over the optic nerve head (arrow). The volume is increased into the vitreous in a controlled slow way to allow the retina to return to its anatomic position. (Art from Jaypee – Highlights Medical Publishers).



until they exit into the vitreous cavity through the pre-existing anterior retinal breaks. In this manner, perfluorocarbon liquids initially reattach the posterior retina and continue to re-appose anterior retina in a what Bourke and Cooling describe as a “sequential manner”. This mechanism of anterior displacement may eliminate the need for a posterior drainage retinotomy in many cases. Often, subretinal fluids are trapped posteriorly by the use of lighter-than-water tamponading agents such as gas or silicone oil, which force fluids posteriorly as they are introduced into the vitreous cavity. The ability of perfluorocarbon liquids to naturally descend to the most posterior retina also makes them ideal for use in engaging the rolled anterior flap of a giant retinal tear, facilitating the accurate repositioning of the tear.

Optical Clarity

All perfluorocarbon liquids tend to be optically clear and relatively free of sources of reflection or optical aberration, as can be the case with other retinal tamponades. The ability to flatten the retina effectively intraoperatively, and the optical clarity of material allows the application of laser energy to the attached retina during the surgical procedure, thus ensuring adequate laser treatment. Since they do not absorb visible light and have a higher boiling point than the thermal burn, perfluorocarbon liquids are considered a safe medium for the delivery of laser energy. In a study conducted by Bourke and Cooling, they found that the intraoperative use of laser and diathermy tended to raise the

local temperature of preretinal perfluorocarbon liquids to between 35° and 50° C under in-vitro conditions.

Immiscible with Intraocular Fluids

Perfluorocarbon liquids vary slightly in their miscibility with water. The ability of the material to resist incursion by blood or intraocular fluids makes it a valuable aide in improving visibility in cases involving heavy or uncontrolled bleeding. Perfluorocarbon liquids can also be used as a “unit”, making them helpful in retrieving intraocular or crystalline lenses by floating them off the retina and up into the pupillary space.

Interfacial Tension

Perfluorocarbon liquids have a relatively low surface tension (14–17 dynes/cm) and correspondingly high interfacial tension in water. This property makes the occurrence of subretinal perfluorocarbon liquid somewhat less likely than with silicone oil due to a higher perfluorocarbon-water interfacial tension than that of silicone-water.

Viscosity

Perfluorocarbon liquids vary greatly in their viscosity. The ideal material for intraocular use should have a very low viscosity, making it easy to inject and remove completely at the end of the procedure. Having a perfluorocarbon with a low viscosity also makes the



management of subretinal migration much easier and safer to remove in the event that this should occur.

Refractive Index

The ability to accurately control intraoperative perfluorocarbon liquid is dependent in large part on the surgeon's ability to visualize the material in the eye. Perfluorocarbons vary widely in their refractive index. Some, like perfluoro-n-octane, have an index significantly different than aqueous (1.27 vs. 1.33). A distinct interface between the perfluorocarbon liquid and aqueous can be clearly visualized. With other perfluorocarbon liquids, such as perfluorophenanthrene, the refractive index is similar to water (1.33) and visualization of the interface is poor. The inability to clearly see the perfluorocarbon-saline interface also makes it very difficult to be sure that all the remaining perfluorocarbon liquid has been removed at the conclusion of surgery.

Vapor Pressure

Just as with the refractive index, the vapor pressure rates (volatility) of the various perfluorocarbon liquids differ greatly. During the process of removal, it is a distinct advantage to have a material with high vapor pressure (perfluoro-n-octane). During fluid-air exchange, any residual layer of perfluoro-n-octane will usually evaporate

after aspiration of all visible perfluorocarbon liquid. The vaporized liquid exits with air via the sclerotomy sites. Perfluorocarbon liquids with lower vapor pressure rates are less volatile, and extensive irrigation of the retina with saline is necessary to insure that all the material has been removed at the conclusion of the surgery.

Tamponade Force

Perfluorocarbon liquids have a tamponade force greater than that of silicone oil. This force has been described as a "third hand", providing a hydrokinetic tool for opening a narrow or closed funnel retinal detachment with PVR, or for stabilizing the retina during peeling of epiretinal membranes. However, it is important that the tamponade force not be too great, particularly in procedures involving an atrophic retina where iatrogenic breaks could easily occur.

The chemical and physical properties of perfluorocarbon liquids offer a major technical advance in the area of vitreoretinal surgery. Although not appropriate as a long-term vitreous replacement, the clinical study and subsequent FDA approval of one such material PERFLUORON (purified perfluoro-n-octane liquid-Alcon Laboratories), has established the safety and efficacy of this particular perfluorocarbon liquid for the management of retinal detachments associated with trauma, proliferative vitreoretinopathy and/or giant retinal tear.



WORKING WITH PERFLUOROCARBON LIQUIDS

The physical and chemical properties of certain types of perfluorocarbon liquids makes them ideal surgical tools in vitreoretinal surgery. As our clinical experience has grown, we have come to realize that its usefulness may someday only be limited by the ability of the retina to regain function. Listed below are some of the “tips” that we have learned, along with several things that need to be considered when working with perfluorocarbon liquids.

Preparation and Handling of Perfluorocarbon Liquids

The unique physical (immiscibility) and chemical (volatility) properties of perfluorocarbon liquids (PFCL's) make them extremely difficult to adequately sterilize. PFCL's are commercially sterilized and re-sterilization should not be attempted. The 0.22 micron disc filters that are routinely used in surgery are not adequate to handle large (5 ml or more) volumes, and thus are not intended for that use. These filters are included in some approved perfluorocarbon liquid packaging to trap and remove any “cored” stopper material that might accidentally be drawn up into the PFCL syringe. Also, as we all know, these filters do not address the problem of viral contamination, since viruses are smaller than the filter pore size.

The filter material in the disc filters tends to trap from 0.3 to 0.5 ml of fluid as the perfluorocarbon liquid is filtered, so if the surgeon is concerned about not having an adequate volume of PFCL to complete the case, the filter might not be used.

After the PFCL is drawn up and transferred to the sterile field, there are a few precautions that can be taken to avoid the loss of any PFCL prior to its infusion. The use of a small cannula (25 ga. or smaller) will avoid evaporation through the tip, and make slow controlled infusion much easier to achieve. During storage of the syringe and cannula, always elevate the tip of the cannula to avoid having the material flow out the end. This can easily be done by laying it across another instrument on the Mayo stand. Never expose perfluorocarbon liquids to extreme heat, and store the vials at room temperature.

Surgical Instrumentation When Using Perfluorocarbon Liquids

For best results, it is wise to use perfluorocarbon liquids in conjunction with “Wide Field” viewing systems whenever possible. These systems provide a panoramic view of the eye, even when the pupil is partially constricted, allowing visualization of the peripheral retina and the expanding margin of the PFCL bubble (Figure 3).



Figure 3: Excellent Fundus View With Wide Field Lenses. These contact lenses consist mainly of two different versions, providing a 68 degree and 130 degree field of view of the fundus as shown. The 68o area of fundus visualization is appropriate for the observation of the macular structures up to the vascular arcade and its immediate surroundings. The 130o lens allows a panoramic view of the fundus, and viewing up to 360 degrees of the ora serrata by slightly tilting the lens. Both provide the wide range of excellent visualization necessary during the three port approach, (note endoilluminator, infusion port and pars plana site for third instrument (blue arrow). (Art from Jaypee - Highlights Medical Publishers).

Breaks in the peripheral retina can be seen, and traction can be relieved more thoroughly with such systems. Visibility under air in phakic or pseudophakic eyes is also greatly enhanced. With the opportunity to see the peripheral retina more completely, consideration should also be given to the type of light source to be used.

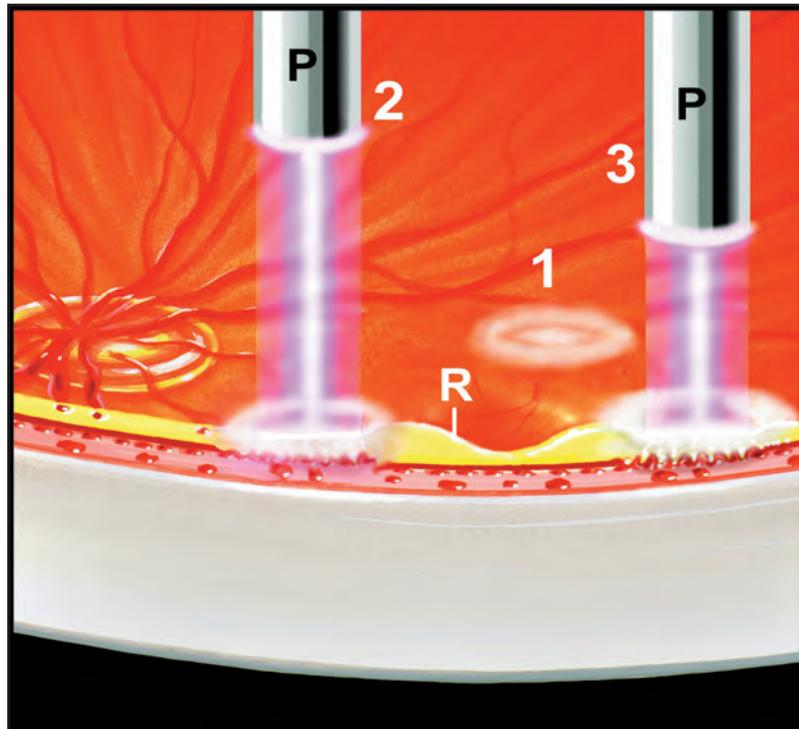
For controlled administration of the PFCL, many surgeons have found that either a small gauge "soft-tipped" extrusion needle or the Chang dual-bore cannula provide the best results. The Chang Cannula helps control intraocular pressure during the infusion of

PFCL's by the use of a side-by-side cannula design that removes BSS or aqueous from the eye in a volume equal to the amount of PFCL infused. Soft-tip cannulas and lighted picks may also be useful in the management of a bullous detachment.

Finally, to take advantage of the ability to perform laser endophotocoagulation under PFCL'S, a multipurpose laser probe, such as Chang Aspirating Laser Probe (with or without soft tip), permits easy and accurate placement of laser energy in the peripheral retina (Figure 4).



Figure 4: Endolaser Does Not Touch the Surface of Retina. The proper wattage to use for endophotocoagulation should result in a faint whitish reaction on the retina (1). These threshold lesions should be obtained with the tip of the laser probe (P) about 2 disc diameters from the retinal surface as shown at (2). (3) A stronger laser reaction on the retina can be accomplished by increasing exposure time or bringing the probe (P) slightly closer to the retina (R). The instrument never touches the surface of the retina, saving adjacent structures from damage. (Art from Jaypee – Highlights Medical Publishers).



Administration of Perfluorocarbon Liquids

Always administer perfluorocarbon liquids slowly, keeping the tip of the cannula just within the meniscus of the expanding bubble, and centered over the optic disc if it is visible.

A small bubble of PFCL will flatten and stabilize the posterior retina, allowing time to evaluate and control the retina anterior to

the PFCL before continuing with membrane removal if necessary.

Continue to administer the PFCL slowly as needed, constantly monitoring the position of the PFCL meniscus as it spreads. Avoid forceful infusion of PFCL, as this may cause retinal breaks.

As the PFCL reaches the anterior portion of the vitreous cavity, reduce the flow of the active infusion line to avoid dispersion and the creation of many tiny PFCL bubbles.

Since PFCL is not miscible with water. If necessary, turn off the infusion line at this point, or lower the bottle height to reduce turbidity.

Sometimes, despite our best efforts, small bubbles of PFCL will form. If they appear beside the larger bubble, wait for a minute or so, and they will often merge on their own. If this doesn't happen, you may encourage their coalescence by gently stroking the surface of the bubbles together with an instrument such as a soft-tip extrusion needle. Be sure to remove any small bubbles before beginning epiretinal mem-

brane removal. Residual membranes can be removed under PFCL, although it is usually preferable to peel membranes anterior to the PFCL bubble (Figure 5). If working beneath PFCL, care should be taken not to lift the retina or tear it.

The low surface tension and correspondingly high interfacial tension of some PFCL'S, such as perfluoro-n-octane, will permit their use over small retinal breaks without fear of subretinal migration, so long as the retina is completely mobile and free of any residual traction.

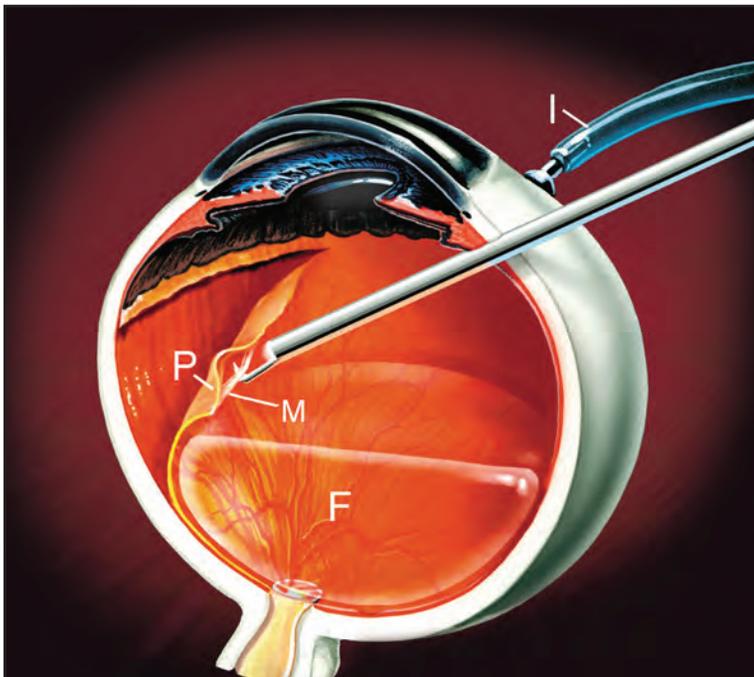


Figure 5: Technique for Removal of Epiretinal Membranes on the Inner Surface of the Posterior Edge of a Giant Tear. As perfluorocarbon liquid (F) is injected, the edge of the posterior flap (P) of the giant tear is monitored. Resistance to unfolding by the PFC liquid may give a clue to the presence of epiretinal membranes on the inner surface of the posterior edge of the tear. Epiretinal membranes (M) on the inner surface may give the edge a rolled appearance and can cause a circumferential shortening along the edge. These membranes should be dissected with a vitreoretinal pic as shown, or if this is not possible, excised (I). (Art from Jaypee – Highlights Medical Publishers).



Remove all retinal traction before increasing the PFCL fill level above any retinal break, paying particular attention to anterior traction. Subretinal membranes tend to become more visible under PFCL'S, but they should be removed anterior to the PFCL bubble only. If residual subretinal traction is noted under PFCL, the PFCL should first be removed by aspiration before attempting to do subretinal membrane removal.

PFCL'S may also be useful in helping you locate posterior retinal breaks that have not been previously visualized. Infuse the PFCL slowly, and as the bubble expands, monitor the peripheral meniscus carefully. Stop infusion of the PFCL when a break is reached by the meniscus, and remove all retinal traction before continuing to fill the eye. If PFCL slips beneath the retina at the break, the PFCL is usually aspirated through the same break it migrated through, using a soft-tip extrusion needle.

Since they are not miscible with blood or other organic compounds, PFCL'S can be used in cases involving active bleeding, such as PDR or vitreous hemorrhage, to improve intraoperative visibility or to contain fresh blood. The blood can be "swept" back from the operative field off of the surface of the PFCL bubble.

Avoiding and/or Managing PFCL Complications

The main complications of perfluorocarbon liquids are subretinal migration and residual

droplets. Subretinal migration occurs when traction on a retinal break is unrelieved, and the level of the PFCL rises above it. As epiretinal membranes surrounding the break are peeled, the lifting of the retina may result in subretinal migration. This can be avoided by careful monitoring of the level of the PFCL as it is injected and rises close to the retinal break.

Always try to keep the PFCL meniscus posterior to the break. A panoramic viewing system can be helpful in visualizing the meniscus as it rises in the periphery. If membrane dissection around a break flattened under PFCL is required, the pulling forces to free the membrane should be exerted tangentially so that the retina is not lifted as membranes are peeled.

Removal of subretinal PFCL is usually done by removing at least part of the pre-retinal PFCL, and then tilting the globe over so that the subretinal bubble will roll near a retinal hole. A soft silicone-tip flute needle can be used to aspirate the PFCL. With a large retinotomy or giant tear, subretinal PFCL can easily be aspirated from under the retinal flap.

Residual droplets of PFCL can be avoided by good visualization during the fluid-air or fluid-silicone exchange. With perfluoro-n-octane, the vapor pressure is high, and any residual layer of PFCL will evaporate as air flushes through the eye. However, it is generally preferable to dry the surface of the retina several times during fluid-air exchange. With low vapor pressure PFCL'S such as perfluorodecalin or perfluorophenanthrene,



the residual layer of PFCL must be irrigated from the surface of the retina under air. A small amount of balanced saline is injected over the retinal surface to allow the residual liquid to form small bubbles which can be aspirated.

Postoperatively, one or two small bubbles of PFCL may occasionally be seen rolling on the retina. These are generally well-tolerated and often become trapped in the ciliary processes.

Larger amounts of residual PFCL (0.5 ml or more), should be removed surgically, since they may cause epiretinal membranes. Bubbles of PFCL in the anterior chamber postoperatively may cause endothelial decompensation and localized inferior microcystic edema or keratic precipitates. These drops can be aspirated using a 30 gauge cannula at the slit lamp under topical anesthetic.

Substantial subretinal retention of perfluorocarbon liquid (PFCL) after vitreoretinal surgery can have drastic consequences on visual outcome in the case of subfoveal location because of its potential direct toxic effects on retinal pigment epithelium (RPE) and photoreceptor cells.¹⁴⁻¹⁸ Most authors recommend that subfoveal PFCL persisting after vitreoretinal surgery be removed when central visual acuity is substantially reduced.¹⁵⁻²⁰

Several techniques have been described. Some authors attempted to perform pneumo displacement by injecting intravitreal gas,¹⁸

direct aspiration of PFCL droplets using a 36-gauge,¹⁸ 39-gauge,¹⁹ or 49-gauge cannula²⁰ via retinotomy adjacent to the droplets on the extrafoveal facing has been also attempted. Irreversible alterations of the pigment epithelium of the macula have been reported as a potential complication of this surgical aspiration procedure.²⁰

INDICATIONS AND TECHNIQUES

Beginning with my first description in 1987 of the utility in vitreous surgery of perfluorocarbon liquids, and continuing with the February 29, 1996 FDA approval based on the data derived from the clinical trials of one such compound (perfluoro-n-octane), ophthalmic literature has extensively chronicled the effectiveness of perfluorocarbon liquids in the intraoperative atraumatic manipulation of intraocular tissues and the displacement of fluids, lens nuclei and intraocular lenses. Several literatures has suggested the following potential applications for the short-term physical and chemical properties of perfluorocarbon liquids:

- Giant Retinal Tear
- Proliferative Vitreoretinopathy (PVR)
- Traumatic Retinal Detachment with Vitreous Hemorrhage and Anterior Retinal Tear
- Management of Dislocated Lens Nuclei
- Management of Dislocated IOL
- Retinal Detachment Associated with Dislocated Crystalline or Intraocular Lenses



- Suprachoroidal Hemorrhage
- Management of Retinal Detachment Following Keratoprosthesis
- Surgical Management of Retinopathy of Prematurity
- Surgical Removal of Submacular Hemorrhage in Conjunction With TPA
- Improving Visualization in Cases of Diabetic Retinal Detachment
- Endophthalmitis
- Retinal Incarceration
- Control of Bleeding During Pars Plana Vitrectomy
- Removal of Intraocular Foreign Bodies
- Treatment of Rhegmatogenous Retinal Detachment
- Retinopathy of Prematurity

Giant Retinal Tear

Prior to the advent of perfluorocarbon liquids in the management of giant retinal tears, texts on the subject by experienced surgeons often described the preoperative preparation of the patient with regard to postoperative positioning and body rolling. Certainly this has changed with the advances in the use of perfluorocarbon liquids and silicone oils during complicated vitreoretinal surgeries.

Scleral buckling alone can be considered in giant retinal tears with posterior flaps that are not inverted and in giant breaks, such as retinal dialysis. The use of perfluorocarbon liquids however should be considered essential for giant retinal tears in which the posterior margin of the tear has inverted and must be manipulated during vitrectomy (Figure 6 and 7). Giant tears complicated

by moderate or severe degrees of proliferative vitreoretinopathy are also best managed with the perfluorocarbon liquids. Traumatic giant tears associated with vitreous or retinal incarceration, or those with severe vitreous or subretinal hemorrhage may also be considered as preferred indications for perfluorocarbon use.

Scleral buckling is not required in eyes with mobile posterior flaps that show no sign of PVR, since there is no vitreous traction on the posterior flap of the tear. An encircling scleral buckle may actually be disadvantageous in these eyes because a decrease in the circumference of the globe resulting from the pressure of the buckle may allow the development of radial folds as the retina flattens. In some cases, the scleral buckle also becomes an insulating barrier that prevents adequate application of additional cryotherapy treatments if they are needed later.

Ultrasonic fragmentation of the clear lens is done if it is subluxated. Many eyes with giant retinal tears are larger in axial length and frequently highly myopic. In these eyes the ora serrata is located more posteriorly, allowing the use of a vitreous cutter to excise the cortical vitreous gel close to the vitreous base, without injuring the lens.

When the pars plana is narrow, or in eyes with a small pupillary opening, it may be advantageous to remove lens so that the peripheral vitrectomy can be more complete, or to visualize the edge of the tear better. Delaying lensectomy until the perfluorocarbon liquid has unfolded the posterior retinal flap may be helpful by preventing any lens

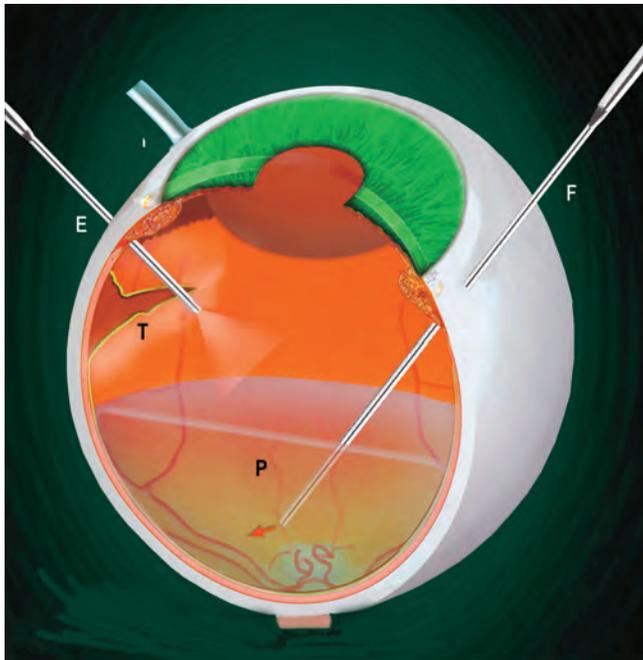
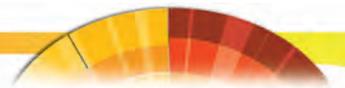


Figure 6: Perfluorocarbon Liquid Application in Giant Retinal Tear. Reattaching the Retina. Shows how the perfluorocarbon liquid (P) is extending through the vitreous cavity and reattaching the retina (D) by the flattening effect. Since PFCL are not miscible with water, the infusion of balanced salt solution (I) may have a tendency to break the PFCL bubble into many small bubbles, reducing visibility. (Art from Jaypee – Highlights Medical Publishers).

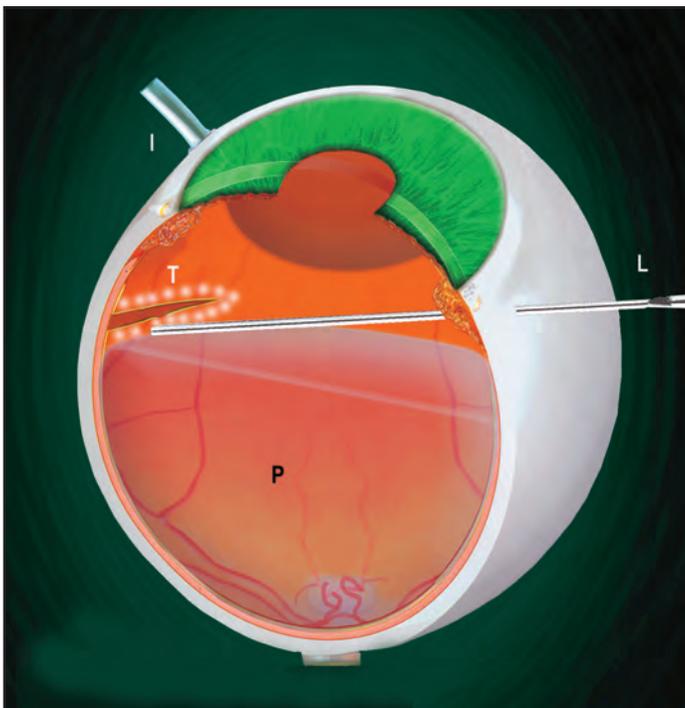


Figure 7: Perfluorocarbon Liquid Application in Giant Retinal Tear. Treating the Tear Margin. Presents how the margin of the tear (T) can be treated with either cryotherapy or laser photocoagulation (L). In most instances, endophotocoagulation is preferred, but when the margin of the tear is too peripheral, cryotherapy or indirect laser photocoagulation is used. Both treatments can be applied through the perfluorocarbon liquid (P), and one row of cryotherapy or two rows of continuous laser are usually sufficient. (Art from Jaypee – Highlights Medical Publishers).



fragments from migrating into the subretinal space.

After the central vitrectomy has been completed and the tear is gently unfolded any posterior epiretinal membranes are removed and pigment clumps on the retina are aspirated using a flute needle with a silicone tip. A small amount of perfluorocarbon liquid (0.5 to 0.8 ml) is injected over the optic disc and macula. The flattening effect is observed, and the retina is examined for preretinal or subretinal membranes, as well as for the position of the macula. A finding of ectopia indicates traction that has displaced the macula in a direction in which membranes have contracted and shortened the retina. Any peripheral membranes should be removed before additional perfluorocarbon liquid is injected. All membrane dissection and peeling should be done ahead of the meniscus of the perfluorocarbon liquid bubble. When subretinal membranes are seen, the perfluorocarbon liquid is aspirated and the membranes are grasped after inverting the retinal flap.

The margin of the tear can be treated with either cryotherapy or laser photocoagulation. In most instances, endophotocoagulation is preferred, but when the margin of the tear is too peripheral, cryotherapy or laser photocoagulation using an indirect ophthalmoscopic delivery is used. Both treatments can be applied through the perfluorocarbon liquid, and one row of cryotherapy or two rows of continuous laser are usually sufficient (Figure 7). Since the retina is flattened by

the perfluorocarbon liquid during treatment, there is minimal dispersion of retinal pigment epithelial cells, and the clumping of submacular pigment epithelial cells sometimes seen after extensive cryotherapy is prevented.

The extended, long-term tamponade agent should now be selected. Perfluorocarbon liquids can be directly exchanged with either gas or silicone oil. In general, giant retinal tears of 180 degrees or less can usually be managed with a gas tamponade, while breaks larger than 270 degrees are probably best managed with silicone oil. When a gas tamponade is chosen, an automated air infusion system should also be used during the air-fluid exchange. A flute or extrusion needle with a soft silicone tip is placed near the margin of the tear. Perform a slow and deliberate fluid-air exchange, stopping frequently to allow the edges of the torn retina to dry as much as possible.

As the air bubble descends, it flattens the anterior retina, expressing the subretinal fluid through the break. All saline at the edge of the break should be carefully removed before proceeding to aspirate the perfluorocarbon liquid posteriorly. This maneuver reduces the chance of slippage of the posterior flap, since any remaining subretinal fluid will tend to flow posteriorly, causing the posterior retinal flap to also slide posteriorly. If a small amount of slippage is encountered, the situation can be managed by injecting a small amount (1.0 to 1.5ml) of balanced salt solution into the vitreous cavity at the end of the operation. The vitreous cavity is then



flushed with 20 ml of a mildly expansile mixture of perfluoropropane gas and air. The patient's head is appropriately rotated into the prone position after the completion of surgery to correct the slippage. Infrequently, the intrinsic elasticity of the detached retina results in extensive slippage and folding under air. When this occurs, the air should be replaced by balanced salt solution, and perfluorocarbon liquid re-injected to reposition the retinal detachment. When the tear is successfully repositioned, direct exchange of the perfluorocarbon liquid for silicone oil will prevent slippage and folding of the retina. As the silicone oil fills the eye, its descending meniscus engages the edge of the tear and prevents slippage because silicone oil is relatively incompressible compared to air.

When silicone oil is selected for extended tamponade, the perfluorocarbon liquid

is directly aspirated as the silicone oil is injected with an automated infusion pump (Figure 8). When the silicone oil is first injected, the soft-tipped flute or extrusion needle is placed anteriorly near the edge of the tear to aspirate all of the saline anterior to the perfluorocarbon. When the silicone bubble contacts the perfluorocarbon liquid, the interface is visible and the perfluorocarbon is then aspirated from an anterior to posterior direction. Due to the much lower viscosity of perfluorocarbon liquid, it is much more easily aspirated than the silicone oil. After the main bubble of perfluorocarbon liquid is removed, small bubbles of perfluorocarbon may be difficult to distinguish from air bubbles that have mixed with the silicone oil during injection.

However, within seconds, the air bubbles will float anteriorly in the silicone oil, while

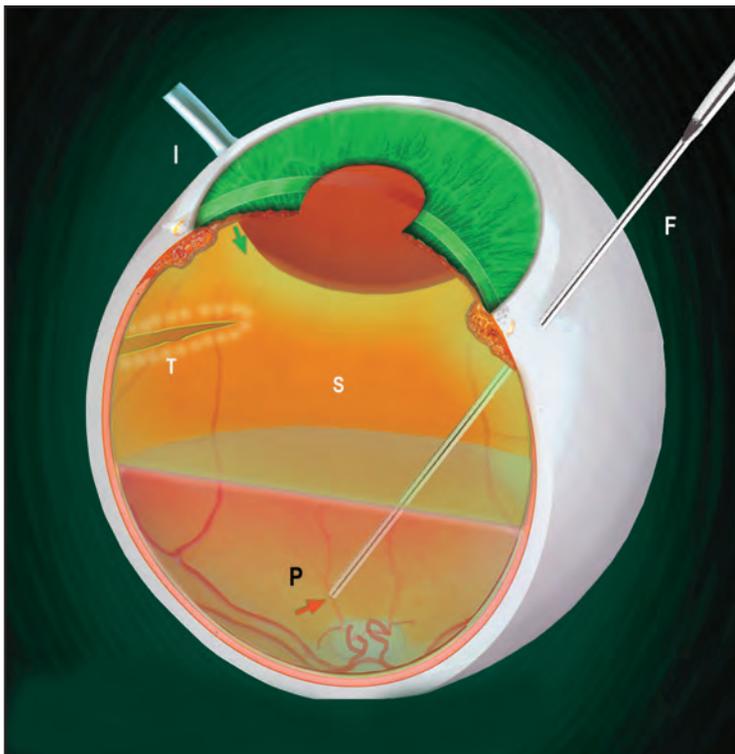


Figure 8: Silicone Oil for Long Term Tamponade. Silicone oil (S) may be employed for long-term retinal tamponade. A soft silicone-tip flute needle (F) can be used to aspirate the PFCL. The silicone oil is then injected by the infusion cannula (I). (Art from Jaypee – Highlights Medical Publishers).



the small droplets of perfluorocarbon liquid will descend onto the surface of the retina where they can be easily aspirated.

Risks

The clinical trials of perfluorocarbon liquids have demonstrated two risks associated with the use of these materials; subretinal migration and residual droplets of the perfluorocarbon liquid postoperatively. Both these events have been reported in cases involving giant retinal tear.

When small bubbles are noted to have slipped subretinally, they can usually be aspirated using a flexible tip extrusion cannula that is passed subretinally through the same break that the perfluorocarbon liquid migrated through, or by stroking anteriorly in a brushing motion with the flexible tip of the cannula in a gentle motion across the retinal surface. Small bubbles that typically lodge in the vitreous base can typically be aspirated with no complications at the time of surgery. Neither subretinal or residual mobile droplets of perfluorocarbon liquids have been associated with any adverse clinical event, however, if the situation warrants subsequent surgical intervention may be necessary to remove them.

Proliferative Vitreoretinopathy (PVR)

As with giant retinal tear, perfluorocarbon liquids are a useful tool for the hydrokinetic manipulation of the retina during vitreous surgery for moderate to severe forms of proliferative vitreoretinopathy. The physical and chemical properties of perfluorocarbon liquids lend themselves well to such intraoperative challenges as opening a funnel detachment, providing counterpressure to facilitate the removal of preretinal membranes, and displaying areas of residual traction.

Surgery is performed by means of a 20, 23 or 25 gauge, three-port, pars plana approach. In phakic eyes, a lensectomy is usually performed. A broad encircling scleral buckle supporting the region of the vitreous base may be added if not already present from previous surgery.

When adherent membranes cannot be removed, a circumferential relaxing retinotomy may be performed anterior to the level of the perfluorocarbon liquid. The stabilizing effect of the perfluorocarbon liquid assists in this maneuver. The flattening effect of the perfluorocarbon liquid, and the subsequent anterior displacement of subretinal fluids often eliminates the need to perform a posterior

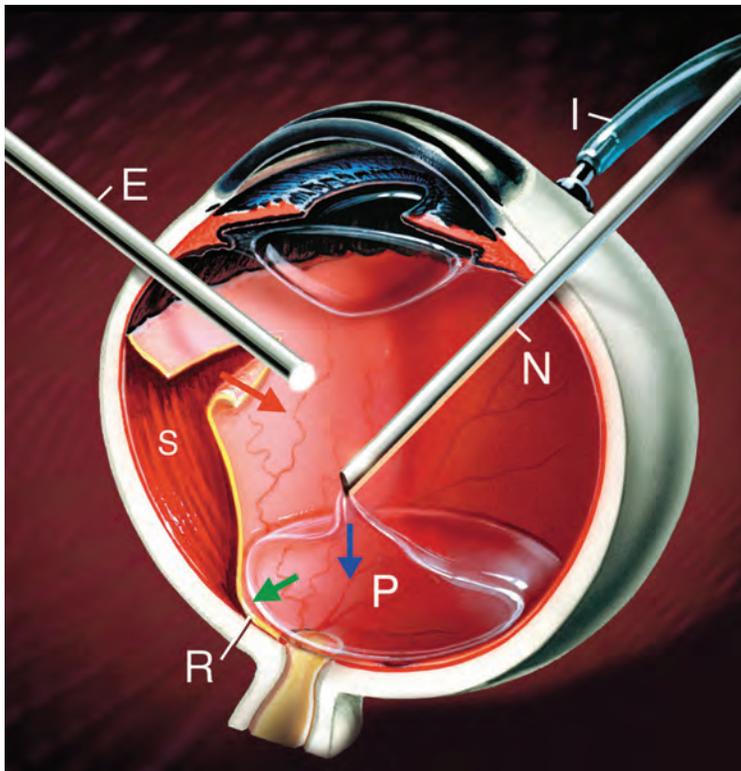


Figure 9: Retinal Reattachment With Perfluorocarbon Liquid in Case of Giant Tear. In the case of retinal detachment with giant retinal tear, perfluorocarbon liquid (P) is injected into the vitreous cavity (N). Because the liquid has a specific gravity greater than water, it gravitates (blue arrow) to the posterior pole. This forces the subretinal fluid (S - red arrows) out through the giant retinal tear. The retina (R) is being forced to reattach (green arrow). Infusion cannula (I). Endoilluminator (E). (Art from Jaypee - Highlights Medical Publishers).

drainage retinotomy, as subretinal fluids are forced upward and out the anterior retinal breaks or tear (Figure 9). By reducing the need for posterior retinotomy to facilitate internal drainage of subretinal fluid, potential complications such as bleeding and the proliferation that often occurs at the retinotomy site is reduced. If traction from subretinal membranes is present, it may be necessary to create a posterior retinotomy sufficient to facilitate their removal. This is done after the removal of a volume of perfluorocarbon liquid sufficient to bring the fill level posterior to any such area of traction.

After all areas of traction have been removed and the posterior retina has been flattened by the perfluorocarbon liquid, a partial fluid-air exchange with internal drainage of subretinal fluid flattens the anterior retina and breaks against the buckle. Laser photocoagulation can be applied through the perfluorocarbon liquid, and laser treatment should be applied for the full 360 degrees over the scleral buckle, and to the areas surrounding all retinal breaks. The air bubble replaces the infusion fluid above the perfluorocarbon liquid, and keeps the posterior retina in place. After completion of



laser, the remaining perfluorocarbon liquid is removed with a 20 gauge flute or soft tip cannula, and the air filled vitreous cavity is replaced with either an air-perfluoropropane gas mixture or silicone oil as the long-term vitreous replacement.

Clinical experience with perfluorocarbon liquids has demonstrated that potential complications related to their use are minimal. Subretinal migration and postoperative residual perfluorocarbon droplets appear to be the only two noted. Subretinal migration can usually be handled in PVR cases by aspirating the material through the same retinal break in which it originally migrated. Small residual droplets are a more common problem postoperatively, perhaps due in part to their ability to be concealed in the peripheral fundus. No postoperative complications have been observed after long-term follow-up for up to two years in the case of the Perfluoron clinical trial. They are best avoided by carefully avoiding dispersion of the perfluorocarbon liquid at the time it is injected. Perfluorocarbon liquids are not tolerated in the anterior chamber, with larger bubbles causing corneal edema within 2-3 days at the site of contact.

Trauma

Blunt or penetrating ocular trauma elicits a broad range of responses, including intraocular bleeding, severe inflammation, fibrous proliferation, and/or cyclitic membrane formation. Retinal detachment may result from any one or a combination of these, or from the injury itself. Further, there is the concept

of “surgical trauma” in instances such as relaxing retinotomies in retinal detachments complicated by proliferative vitreoretinopathy, traumatic detachment or proliferative diabetic retinopathy.

Perfluorocarbon liquids are a useful intraoperative tool during vitreous surgery in the management of complications arising from severe ocular trauma (Figure 10). The indications for perfluorocarbon liquids in penetrating trauma are: vitreous hemorrhage and retinal detachment, expression of liquefied subretinal blood, traumatic proliferative vitreoretinopathy, traumatic giant retinal tears or dialyses, retinal incarceration, and selected intraocular foreign bodies. In cases of traumatic vitreous hemorrhage with retinal detachment, the retina can be flattened and immobilized while opacified hemorrhagic vitreous can be cut and aspirated more safely. Liquefied blood can often be expressed from the subretinal space without making a posterior drainage retinotomy, improving the potential for macular function. In cases of retinal incarceration, perfluorocarbon liquids can be used to open the folds and free epiretinal membranes, within the incarcerated retina. If incarceration is located peripherally, a relaxing retinotomy may be required to free the retina from the injury site.

Often, visualization is an extremely difficult challenge in trauma cases due to excessive intraocular bleeding²¹. Perfluorocarbon liquids can provide improved visibility due to their immiscibility with blood or ocular fluids. Their high specific gravity also may provide some improved control due to the tamponade force of the material.

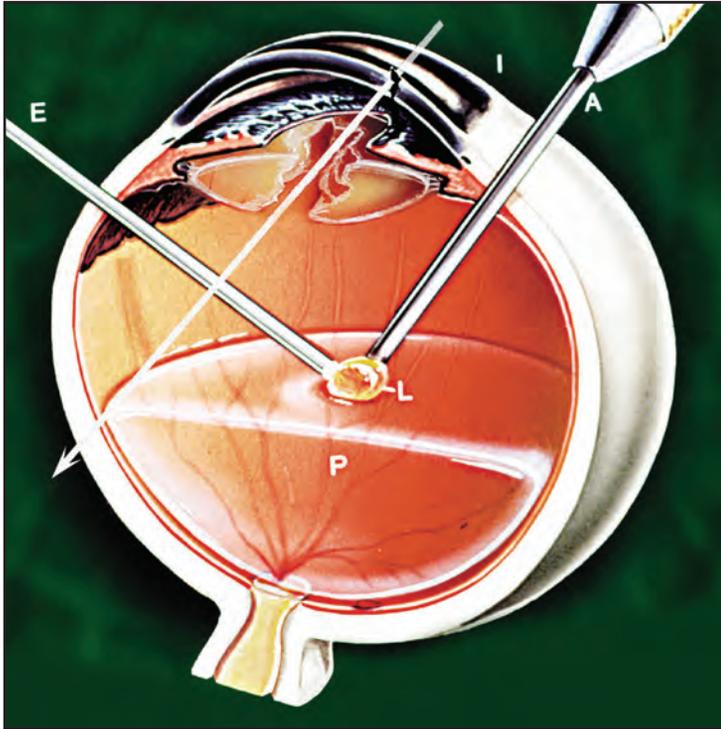


Figure 10: Application of Perfluorocarbon Liquids in Trauma. Improved munitions, which create increasingly smaller fragments, and also non-conventional or unknown munitions, have multiplied the number of blast injuries and fragment injuries in the eye (arrow). It is imperative to explore the posterior pole and evaluate the conditions of the retina before injecting perfluorocarbon liquid (P) and control all subretinal maneuvers. Lens fragment (L), endoiluminator (E), vitrectomy probe (A). (Art from Jaypee – Highlights Medical Publishers).

Long-term retinal tamponade may be obtained by any one of three techniques: perfluorocarbon liquid/air exchange, followed by air-gas exchange; perfluorocarbon liquid/air exchange followed by the injection of silicone oil into the air-filled eye; or direct perfluorocarbon/silicone oil exchange. The first technique is performed in cases receiving a long-term gas tamponade, and the second and third are associated with the use of silicone oil as the long-term vitreous replacement. In all techniques, intraocular irrigation fluid anterior to the perfluorocarbon liquid interface is first removed by aspiration during the initial injection of air or silicone oil. Subsequently, aspirate perfluorocarbon liquid and any residual subretinal fluid at the

anterior-most edge of the retinotomy, working posteriorly along the edge of the retinotomy as the perfluorocarbon meniscus recedes, and allowing adequate time for the edge of the retinotomy to dry as much as possible. This approach allows complete removal of fluid at the retinotomy edge, and helps prevent posterior retinal slippage.

Dislocated Lenses

The popularity of phacoemulsification in cataract and intraocular lens surgery has led to a relative incidence of dislocated crystalline lenses or lens fragments, and subluxated intraocular lenses.

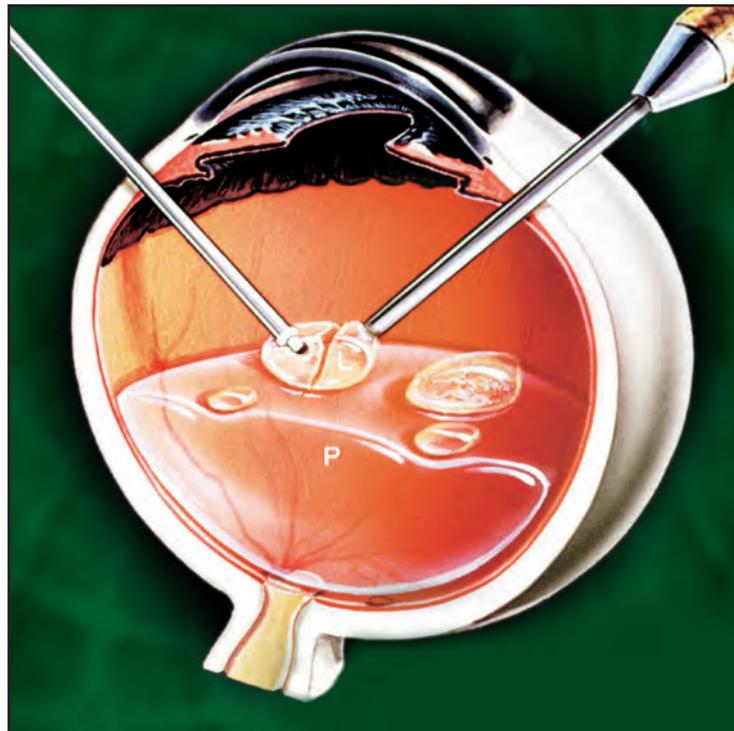


The specific gravity of perfluorocarbon liquids is greater than that of crystalline lenses, polymethylmethacrylate (IOL's), silicone or acrylic intraocular lenses, and allows the surgeon to gently float the dislocated lens or fragment off the retina following a "complete" vitrectomy, by injection of the perfluorocarbon liquid under the object, and by using the previously described techniques for maintaining a single large perfluorocarbon bubble (Figure 11). Once elevated, the lens can be removed via the limbus using a vectus or IOL forceps). Fragmentation of nuclear particles can be performed in mid-vitreous on a cushion of perfluorocarbon liquid, since the perfluorocarbon liquid will

act as a "shock absorber" for the ultrasonic energy. However, it should be noted that the perfluorocarbon liquid bubble tends to have a convex surface, and small particles may tend to gravitate toward the periphery where they become more difficult to detect and manage unless the surgeon has the advantage of a "wide angle" viewing system.

In situations where a posterior chamber IOL requires fixation by suturing, the IOL can be held in position behind the iris plane by the perfluorocarbon liquid, thus helping to avoid the need for the use of forceps or snares.

Figure 11: Use of Perfluorocarbon Liquid for Dislocated Lens. In cases of removal of a hard dislocated lens, perfluorocarbon liquid (P) can be placed in the eye. Lens fragments float on top of the liquid at a safe distance from the retina. Here a large lens piece (L) is cracked and aspirated with the ultrasonic tip and manipulated with vitrectomy probe. (Art from Jaypee – Highlights Medical Publishers).





Where retinal detachment and a dislocated lens both exist, perfluorocarbon liquids simultaneously combine lens flotation with subretinal fluid displacement via anterior breaks, often avoiding the need for a posterior retinotomy.

It must be stressed that a complete vitrectomy is required, including generous clearance of basal vitreous before the infusion of perfluorocarbon liquids in any eye. In the presence of an incomplete vitrectomy, the lens or fragment will often become entrapped in basal gel, and significant residual amounts of the perfluorocarbon liquid may be trapped and retained in the basal vitreous. Following vitrectomy, a careful fundus examination should be done either intraoperatively or postoperatively to rule out retinal breaks.

Conclusion

The clarity of perfluorocarbon liquids, with a refractive index close to that of water, allows the use of a conventional contact lens for vitreous surgery while the low viscosity facilitates tissue manipulation, injection, and removal. Perfluorocarbon liquids represent the only class of heavier-than-water vitreous substitutes, but current agents cannot safely remain in the eye for an extended time. Research efforts are therefore focusing on long-term tamponading vitreous substitutes that can support the inferior retina. This would reduce the need for prolonged postsurgical face-down positioning and may increase the anatomic success rate in management of PVR by displacing proliferative cells from the inferior quadrants of the retina.

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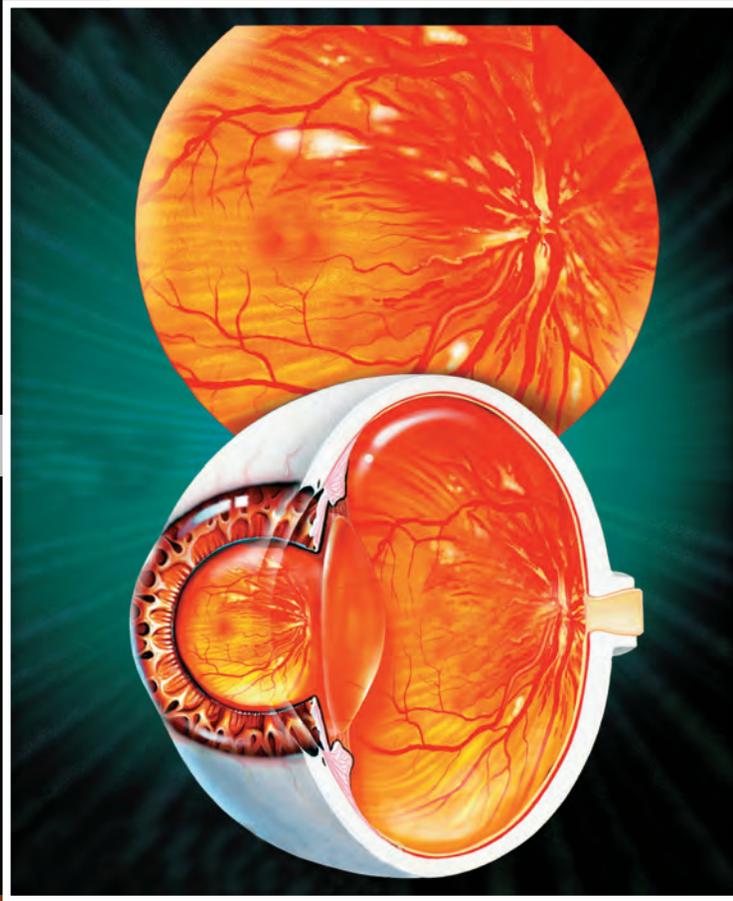
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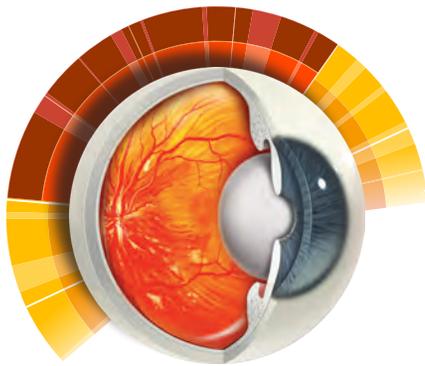
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Section 4

Retinal Vascular Diseases



11

Classification and Management of Diabetic Retinopathy

JUAN VERDAGUER T., MD.,
JUAN IGNACIO VERDAGUER D., MD

Global prevalence of diabetic retinopathy is dramatically increasing. The most rapid growth will occur in low and middle income countries. Blindness from diabetic retinopathy will also dramatically increase, unless effective interventions take place. A large proportion of diabetic patients do not know they have diabetes and many patients with known diabetes have poor glycemic control as well as insufficient treatment of arterial hypertension and other risk factors for diabetic retinopathy.

Evidence-based treatment for diabetic retinopathy (DR) is available. Clinical trials, such as the Diabetic Retinopathy Study (DRS), the Early Treatment Diabetic Retinopathy Study (ETDRS) have demonstrated that laser treatment can reduce severe vision loss by 90%.

A clinical classification of diabetic retinopathy, describing different levels of severity of the disease is critical in decision-making and appropriate management of diabetic retinopathy by the ophthalmologist. The gold

standard for classification of DR is the ETDRS severity scale. Each level of the ETDRS classification is based on the risk of progression to sight-threatening retinopathy. This scale is most useful in a research setting, but is not practical for every day use in clinical practice; each of 20 ophthalmoscopic lesions has to be graded in a scale from 2 to 6 levels; the grading requires comparison with standard photographs; the scale has too many levels, impossible to remember in a clinical setting.

For those reasons, the American Academy of Ophthalmology launched the Global Diabetic Retinopathy Research Group, inviting 31 experts from 16 countries around the world, to develop consensus on an international clinical classification of DR that could be used around the World.⁽¹⁾ This clinical classification has a strong scientific basis and was based on the ETDRS scale and the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR).



By categorizing DR and diabetic macular edema (DME), the clinical classification provides a framework for improved communications among ophthalmologists, endocrinologists and other care providers. Specific treatment recommendations for each category can be formulated.

Treatment recommendations may differ slightly in different regions of the world. The classification is most useful also for screening of diabetic populations.

International Clinical Classification of DR

1. *No apparent retinopathy.* No abnormalities related to DR found on dilated ophthalmoscopy. If the glycemic control is good, follow up examination at 24 months.
2. *Mild non proliferative diabetic retinopathy.* Microaneurysm only. (Equivalent to level 20 of the ETDRS scale). Educate patient on importance of maintaining good glycemic control and monitoring HbA1c and the importance of reducing blood pressure and serum lipids if necessary. Fluorescein angiography is not indicated. Follow up at 12 months.
3. *Moderate non proliferative diabetic retinopathy (moderate NPDR)* (Figure 1). More than just microaneurysms but less than severe non proliferative diabetic retinopathy. This patients may have cotton wool spots and lipid deposits (“hard exudates”), retinal



Figure 1: Moderate NPDR. Retinal hemorrhages and cotton wool spots.

hemorrhages (but less numerous than 20 intraretinal hemorrhages in the four quadrants). Venous beading (irregular dilation of the retinal veins), but only in one quadrant. Moderate NPDR is equivalent of level 35 of the ETDRS scales (probability of progression to proliferative DR: 5.4% in one year). It also includes level 43 (11.9 probability of progression to DR) and level 47, with beading in one quadrant. Level 47 was a higher risk of progression to PDR (26.3%).

Because the probability of progression to PDR is relatively low, there is universal consensus: laser photocoagulation is not indicated in this category if there is not macular edema. If the patient is under the care of an endocrinologist or



generalist, the patient should be referred to an ophthalmologist. Follow up is 6 to 12 months. Patients with venous beading in one quadrant should be carefully monitored. Optimization of medical treatment and education of the patient is mandatory. Fluorescein angiography is not generally indicated, unless there is macular edema or the retinopathy looks too florid. Fundus photography may be valuable to document progression of the disease.

One major problem in the difficulty in recognizing IRMA (Figure 3) and, in a lesser degree, venous beading by observers not fully trained in ophthalmoscopy. Recognizing IRMA (Intraretinal Microvascular Anomalies) requires a very careful and prolonged examination. There are intraretinal small vessels of tortuous design, they are different to retinal neovascularization, which grows above the retina and leaks on fluorescein angiography. In some patients, biomicroscopic examination with a contact lens will be necessary to



Figure 2: Severe NPDR a) severe hemorrhages in 4 quadrants. b) Venous beading c) IRMA.

4. *Severe non-proliferative diabetic retinopathy (severe NPDR)*. Any of the following: more than 20 intraretinal hemorrhages in each of four quadrants; definite venous beading in 2 or more quadrants; prominent intraretinal micro vascular abnormalities in one or more quadrants and no signs of proliferative retinopathy. The simplified method of defining severe NPDR is "4: 2: 1 rule (Hemorrhages, 4 quadrants, venous beading 2 quadrants and definite IRMA 1 quadrant) (Figure 2).

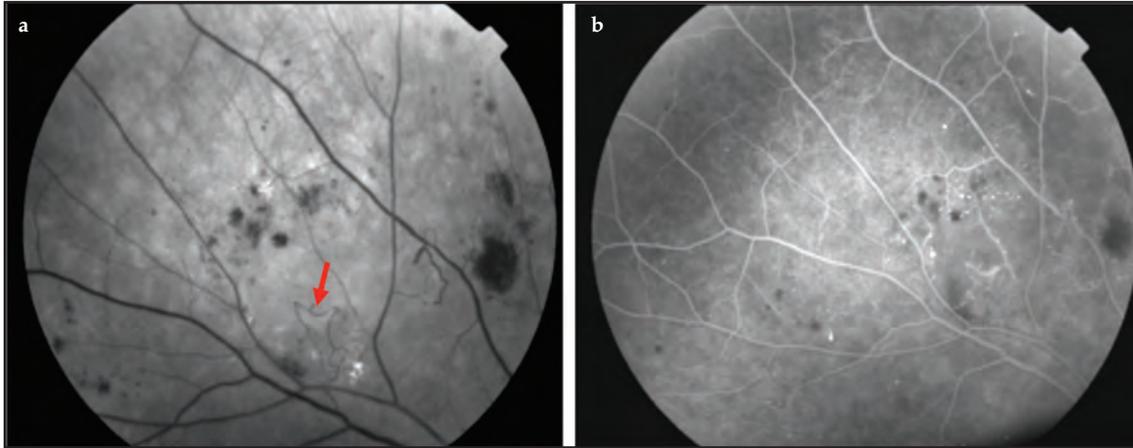


Figure 3: a) Intraretinal microvascular abnormalities (IRMA). b) Fluorescein angiography shows staining of the vessels wall but not leakage. Note area of capillary non perfusion adjacent to IRMA.

confirm the presence of IRMA. However, data from the WESDR demonstrated that the use of hemorrhages alone was not as strongly related to risk of progression to PDR as hemorrhages plus IRMA and venous beading.

Venous beadings are localized dilation of the venous wall (Figure 4). Venous loop can also be observed; the vein shows a loop or divides in two secondary channels that reunite distally.

These venous abnormalities are associated with severe ischemia and are more frequently observed in the nasal fields.

The risk of progression to PRN of severe NPDR is 50.2% in one year and 14.6% to high risk PDR. If the three characteristics are present (severe intraretinal hemorrhages x 4 quadrants + venous beading x 2 quadrants + IRMA x 1 quadrant), the risk of progression to high risk PDR is 45% in one year.

Severe NPDR is a sight threatening condition, with a high risk of progression. Pan retinal laser photocoagulation should be considered if:

- Poor compliance
- Advanced proliferative disease in the fellow eye
- Impending cataract surgery
- Poor glycemic control
- Advanced renal disease
- Extensive capillary closure at wide-angle fluorescein angiography.
- Pregnancy

The benefit of early scatter pan retinal photocoagulation is greater in patients with type 2 Diabetes. Treatment should be considered in patients with severe NPDR and Type 2 diabetes.

International guidelines recommend scatter pan retinal laser photocoagulation only in the above mentioned circumstances; however, the threshold for initiating laser treatment is a decision that should be

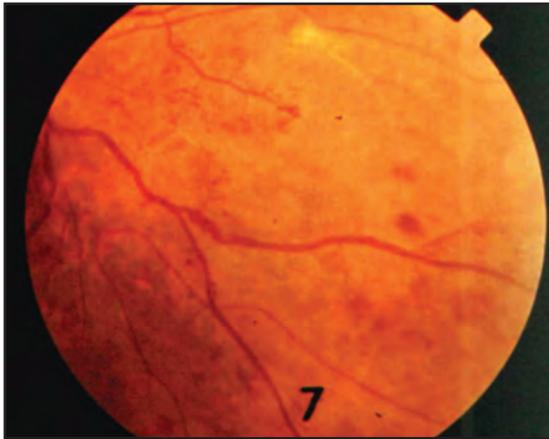


Figure 4: Venous beading.

made by each country (WHO consultation in Geneva, November 2005). In Latin America laser pan photocoagulation should be considered for patients with severe NPDR, because of poor patient compliance; besides, follow up every 2 to 4 months, as recommended if laser is deferred, is a completely unrealistic recommendation for developing countries, with overcrowded facilities.

Panoramic fluorescein angiography should ideally be ordered in every case of severe NPDR

5. *Proliferative diabetic retinopathy (PDR)*. One or more of the following: neovascularization of the retina or disc and vitreous or preretinal hemorrhage. This category includes the following:

- a) Mild PDR, with retinal neovascularization, less than $1/2$ disc area in size in one or more quadrants (ETDRS level 16).
- b) Moderate PDR with retinal neovascularization greater than $1/2$ disc area and optic disc neovascularization less than $1/3$ disc area (ETDRS level 65).
- c) High risk PDR (Figure 5). High risk characteristics for severe visual loss are:
 - New vessels within 1 disc diameter of the optic nerve head that is larger than $1/3$ disc area.
 - Vitreous or preretinal hemorrhage.

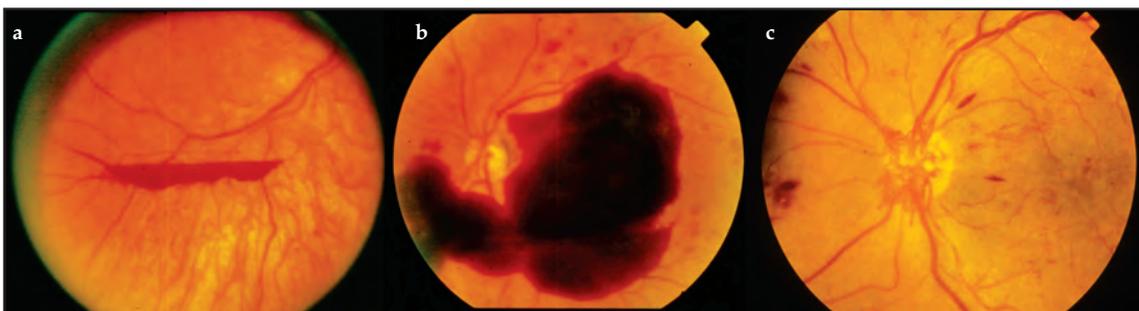


Figure 5: Proliferative diabetic retinopathy with high risk characteristics. a) and b) preretinal hemorrhages. c) neovascularization of the optic disc.



- d) Advanced PDR with fibrovascular proliferations, (Figure 6) retinal detachment (tractional or rhexmatogenous) and complete obscuration of the ocular fundus by vitreous hemorrhage.

Fluorescein angiography is not mandatory in PDR, unless macular edema is present.

Patients with high risk PDR should receive scatter pan retinal photocoagulation immediately after diagnosis. In developing countries, pan retinal scatter photocoagulation should also be considered for PDR without high risk characteristics, because patients may return many months later with an advanced form of PDR.

In patients with advanced PDR not amenable for photocoagulation, vitreous surgery may be indicated. In patients with PDR and macular edema, the ophthalmologist may choose to treat the macular edema first and perform the pan retinal photocoagulation later. If the PDR

is sight-threatening, combined focal and pan retinal photocoagulation at the first session should be considered. Pan retinal photocoagulation should be divided in at least two sessions.

Scatter Laser Treatment of Diabetic Retinopathy (Pan Retinal Photocoagulation or PRP)

Information to the Patient

- PRP reduces the probability of vision loss, but some patient's vision may worsen in spite of laser treatment.
- In patients with disc/retina neovascularization, the risk of vitreous hemorrhage persists after PRP, since regression of neovascularization is slow. The vitreous hemorrhage is not caused by the laser treatment. PRP may induce moderate

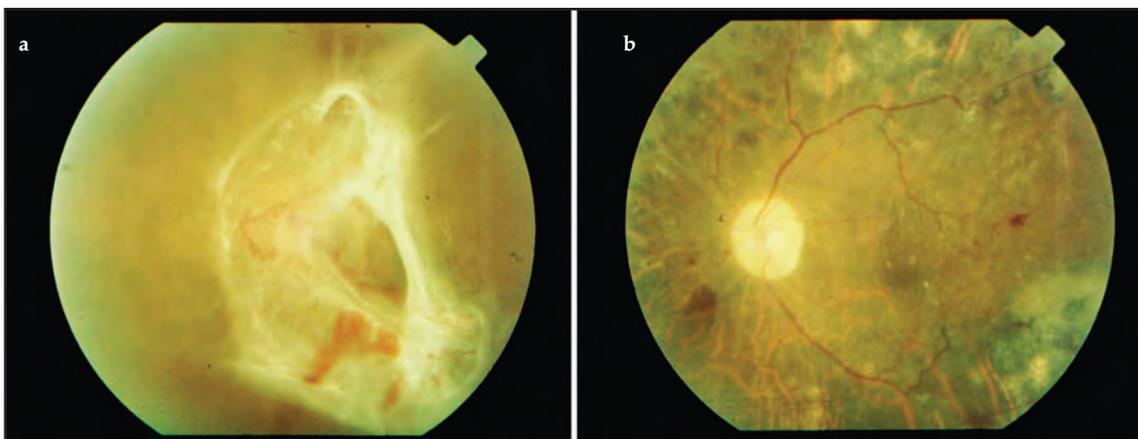


Figure 6: Advanced PDR with fibrovascular proliferation. a) before b) after pars plana vitrectomy.



vision loss, restriction of the visual fields and nictalopia; however it has been demonstrated that laser is effective at preserving vision in the long run, as compared to no treatment in a scientifically impeccable study of more than 1700 patients.⁽²⁾

- For a successful result patients must return for follow-up visits, since additional laser is needed often. Optimization of medical control of glucose, blood pressure and anemia are essential in the care of their disease.
- A handout may be effective in patient's education.

Lenses

The Goldmann three-mirror lens is seldom used for PRP. However, its high magnification and resolution allows precision laser treatment at the posterior pole and the side mirrors may be used for treatment of specific lesions at the mid periphery or periphery of the retina. The Goldmann lens gives an upright image.

Wide angle lenses are usually employed in PRP. These lenses provide a wider field of view, with an inverted image. Wide-angle lenses differ in image magnification, laser spot magnification factor and field of view (Table 1).

Lenses	Field of View (static)	Axial image Magnification	Magnification of spot in retina (times)
Mainster Standard*	90°	0.95	1.05x
Mainster Wide Field	128°	0.46	1.50x
Volk Trans Equator	120-125°	0.49	1.43x
Volk Quadra Aspheric	130-135°	0.27	1.92x
Rodenstock Pan Funduscope	120°	0.51	1.41x
Mainster PRP 165*	165°	0.51	1.96x
Volk Super Quad 160	160°	0.27	1.93x

* Ocular Instruments



The wider the field of view, the smaller is the image magnification.

Of lenses in Table 1, the Mainster standard is the less appropriate or PRP, given the small field of view 90°, but can be used for treatment at the posterior pole. All other lenses mentioned in Table 1 are quite appropriate for PRP.

The author uses routinely the Mainster Wide-Field for PRP, because of its high resolution. It has a field of view of 118° that can be increased to 127° with appropriate eye movements. The magnification of the laser spot in the retina is 1.5x, that is to say for a laser spot size of 200 μm , the size of burn in the retina will be 300 μm ; for a spot size of 350 μm , the size of the burn will be 500 μm .

I usually complement the treatment with the Mainster PRP 165 lens or the Quadraseric, which have the widest field of view, even though the resolution is not as good. Treatment with this lens up to periphery is especially important in treating proliferative diabetic retinopathy with high risk characteristics.

Anesthesia

PRP can usually be performed under topical anesthesia. However, some practitioners may prefer retrobulbar or peribulbar anesthesia. Retrobulbar or peribulbar anesthesia may be necessary in patients that do not tolerate the procedure.

Some degree of discomfort or pain is experienced by most patients. Most of the time the procedure can continue using simple measures, such as lowering the pace of the applications, increasing the size of the spots, avoiding the long ciliary nerves at 3 and 9 o'clock, and kindly reassuring the patients.

Laser Wavelengths

Argon green, Diode laser (810 nm) and double-frequency Nd: YAG (green=532 nm) or Krypton (red) and dye lasers seem to be equally effective in the treatment of proliferative retinopathy.

The diode laser, as well as the red laser, penetrates better lens opacities and blood in the vitreous and are less absorbed by blood in the retina. In cases of cataract or vitreous hemorrhage, diode or red laser may be more useful. However, it penetrates deeper in the choroid and its use may be more painful.

It appears there are not practical advantages of specific wavelengths in the treatment of diabetic retinopathy. The extent of photocoagulation is more important than the wavelength used.

Treatment Technique and Parameters

It is important to realize that the **size of the burn** in the retina depends, not only of the size of the laser spot, but also of the



magnification of the lens and on the power and duration of the laser application, the transparency of the media and the pigmentation of the eye.

It is not possible therefore, to define the number and size of applications in performing PRP. Nor can we define the power of applications, since the power needed to obtain a burn in a pseudophakic is much lower than the required power for photocoagulation of the retina in a patient with lens or vitreous opacities. All that can be said is that the power is the minimum necessary to obtain a burn of medium intensity or gray-white (not "chalk white").

The Early Treatment Diabetic Study Research Group⁽³⁾ developed a protocol for scatter laser treatment that may serve as a general guideline for PRP (Table 2).

Size. If we are using a wide-angle lens, a spot size of 350 μm at the retina will be magnified to a burn of 500 μm at the retina, if we are using the proper power. If the power is too low, the burn will be smaller.

Exposure. We prefer an exposure of 0.2 seconds.

Number. The number of applications will change from patient to patient. Borders for treatment are one disc diameter nasal to the disc, just outside the temporal arcades and 4 disc diameters temporal to the fovea, up

to equator and beyond, if possible. Burns should be placed 1/2 to 1 burn apart. We perform the basic procedure in two sessions, starting with the nasal retina if there is not impending risk of vitreous hemorrhage; if this is the case, we start for the inferior half of the retina. Patches of retinal neovascularization are treated with overlapping burns (Figure 7). After completing the two sessions, that may require 1200-1600 applications, the patient is observed and the need for additional treatment is determined at 45 to 60 days. Re-treatment is indicated if new vessels fail to regress or continue to grow despite initial treatment.

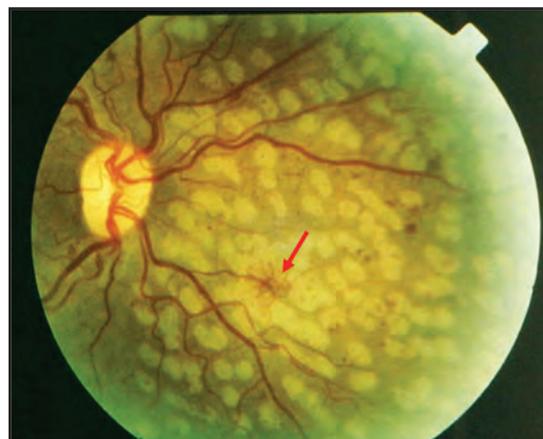


Figure 7: Pan retinal photocoagulation, full. Only the nasal side was treated in the first session. Overlapping burns over a patch of retinal neovascularization (arrow).



Table 2
ETDRS technique for full PRP

Size	500 μm (at retina)
Exposure	0.1 seconds
Intensity	moderate
Number	1200-1600
Placement	1/2 burn apart > 2 disc diameters from fovea out to equator
Number of episodes	≥ 2
Lesions treated directly	patches of NVE* <2 disc areas
Indication for follow-up treatment	Recurrent or new NVE or high risk proliferative retinopathy
*NVE: neovascularization elsewhere (outside disc)	

Dosimetry of laser treatment varies according to the severity of retinopathy; in eyes with proliferative diabetic retinopathy with high risk characteristics, full PRP will be given up to the retinal periphery. Anterior segment neovascularization, rapid disease progression on associated signs of retinal ischemia, such as venous beading and IRMA and extensive capillary closing at the panoramic fluorescein angiography are also indication for heavy, full PRP.

In eyes with severe non proliferative diabetic retinopathy or initial proliferative diabetic retinopathy in which PRP was indicated, because of the accumulation of risk factors for progression or poor compliance, a "mild" scatter photocoagulation may be performed, with separation of burns (one or two burns apart), as initial treatment.



Complications

After PRP, the patient may experience decreased vision that usually resolves in a few days. However, some patients may lose 1 or 2 lines of visual acuity. A side effect associated with PRP includes a decrease in night vision, color vision and restriction of the visual fields. Driving at night or through a tunnel may become hazardous. Exudative retinal detachment or chorioretinal effusion is only observed when all treatment is delivered in one session, technique that we do not advise.

DIABETIC MACULAR EDEMA

Evaluation of Diabetic Macular Edema (DME)

Diagnosis and rational treatment of DME requires the following:

- A. **Stereoscopic examination** of the macula at the slit lamp with a plane-concave lens such as the Goldmann lens.
- B. **Fluorescein angiography (F-A)**. Once the diagnosis of DME is made biomicroscopically, a fluorescein angiogram should be performed. F-A may show well defined areas of leakage from microaneurysms or dilated capillaries (Focal leakage) or

may show wide spread leakage from the macular retinal capillaries (Diffuse leakage), due to a break down of the inner blood-retinal barrier. Cystoid macular edema will occur if the leakage is massive, with pooling of dye in the outer plexiform layer in the late phase of the angiogram.

Leakage of dye on F-A is not always associated with edema or thickening of the retina (if the rate of clearance of fluid out of the retina exceeds the rate of fluid ingress).

F-A may show small ischemic areas or a definite ischemic maculopathy, with an enlargement of the Foveal Avascular Zone (FAZ).

- C. **Optical Coherence Tomography (OCT)**. OCT allows an objective assessment of macular thickness and rules out macular traction. It reveals the presence and extent of vitreomacular traction that may not be detectable with fundus biomicroscopy.

OCT also reveals the presence of subretinal fluid accumulation with or without vitreous traction.

DME: Classification and Indications for Laser Treatment

The Global Diabetic Retinopathy Project Group⁽¹⁾ described a severity scale for DME,



defined as retinal thickening or hard exudates at the posterior pole:

- Mild DME: some retinal thickening or hard exudates in the posterior pole, but distant from the center of the macula.
- Moderate DME: retinal thickening or hard exudates approaching the center of the macula, but not involving the center.
- Severe DME: retinal thickening or hard exudates involving the center of the macula.

Laser treatment is not indicated in mild DME, but should be considered in moderate and severe DME, that is, if retinal thickening or hard exudates threaten or involve the center of the macula.

This classification is derived from the ETDRS classification (Table 3). The ETDRS proved that laser treatment reduced visual loss in patients with clinically significant macular edema and less severe retinopathy. Therefore, treatment should be considered for clinically significant macular edema; non clinically significant DME should be observed.

Table 3

ETDRS Classification of Diabetic Macular Edema

1. Non clinical significant.
2. Clinically significant.
 - a) Retinal thickening or hard exudates associated with retinal thickening involving the center of the fovea.
 - b) Any retinal thickening or hard exudates adjacent or retinal thickening extending within 500 μm of center of fovea.
 - c) Retinal thickening involving one disc area or more of retina, part of which is within one disc diameter (DD) of center of fovea.



Medical Treatment

Once a diagnosis of clinically significant DME is made, our first concern should be to check the medical condition of the patient. DME is more likely to be present in individuals with hypertension, high glycosylated hemoglobin and proteinuria.⁽⁴⁾ Retention of water by any cause may aggravate DME. High serum lipids are associated with vision loss due to macular edema and retinal hard exudates.⁽⁵⁾

The above mentioned risk factors for DME should be addressed and corrected, when possible, before considering laser treatment for DME.

Information to the Patient

- Laser photocoagulation reduces the risk of vision loss by 50%. Treatment is more effective at preserving than restoring vision.
- Re-treatment may be necessary.
- Patients may have paracentral scotomas.
- Very advanced and long standing cases do not benefit significantly.

Treatment of Diabetic Macular Edema

Laser photocoagulation is the current standard of treatment for DME. The ETDRS study evaluated the effects of argon laser photocoagulation in a prospective, randomized multicenter clinical trial. Eyes assigned to immediate focal photocoagulation were half as likely to lose 15 or more letters on the ETDRS chart compared to eyes assigned to deferral of photocoagulation (12% vs. 24%) at three years. In eyes with an initial visual acuity of 20/40 or more, an improvement in visual acuity of 5 or more letters (more than one line on the ETDRS chart) was much more frequent in eyes assigned to treatment. Improvement of visual acuity by 15 letters was uncommon (<3%).⁽⁶⁾

The ETDRS recommended direct treatment to cover areas of diffuse DME and capillary non perfusion. For focal treatment of retinal microaneurysms a small spot of 100 μm should be used. (We think that a smaller spot of 50 μm is potentially dangerous).

Focal versus Diffuse Diabetic Macular Edema

There is not a clear, universally accepted definition of focal DME and diffuse macular edema. Many cases have mixed features,



making a distinction difficult.⁽⁷⁾ These terms should be used with caution.

Focal DME. These patients usually show lipid exudates associated with retinal thickening, often in the form of circinate rings. On fluorescein angiography these eyes have a

high proportion of leakage originating from microaneurysms (Figure 8). The ETDRS graded the source of leakage for classification of DME as focal or diffuse. Eyes with 67% or more of leakage associated with microaneurysms were classified as focal.⁽⁸⁾

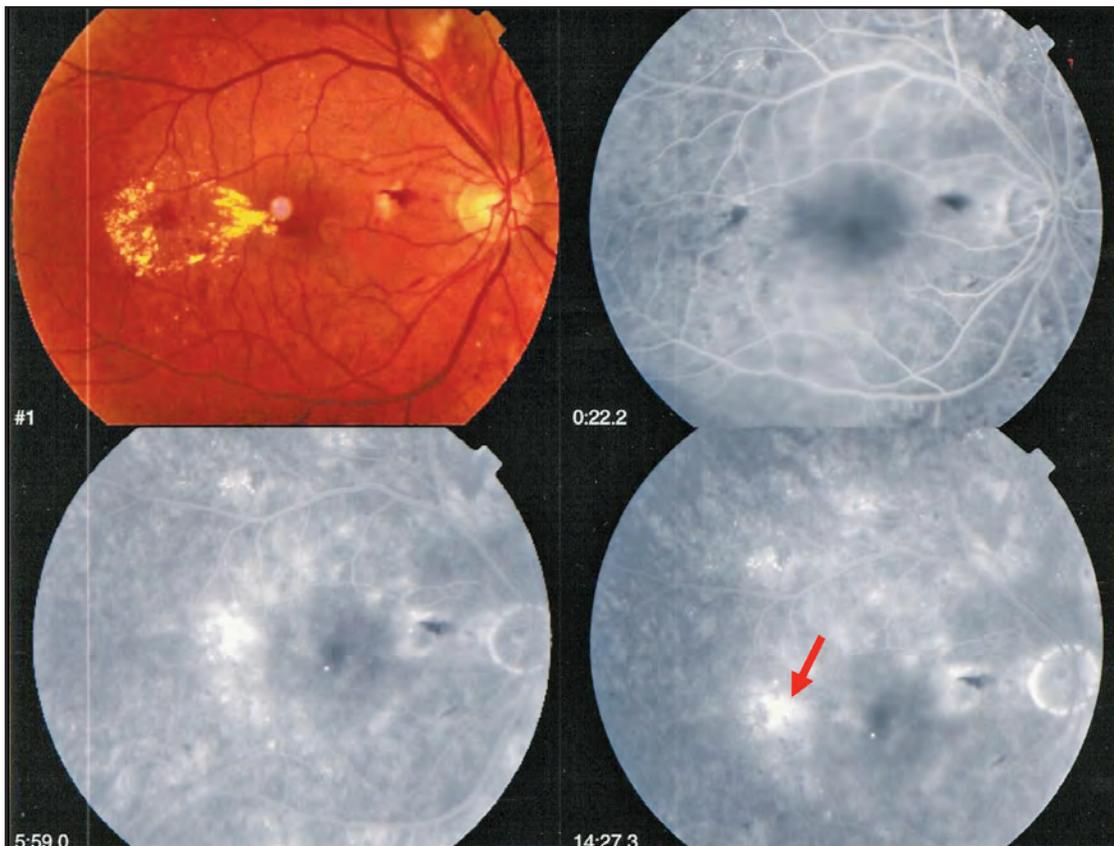


Figure 8: Focal DME. Circinate ring and focal area of fluorescein leakage temporal to the fovea.



OCT will show retinal thickening in the area of the leaking microaneurysms or capillary. The OCT map, will show the thickened area, where laser treatment should be

concentrated (Figure 9). Isolated areas of hot colors are surrounded by larger areas of cool colors.

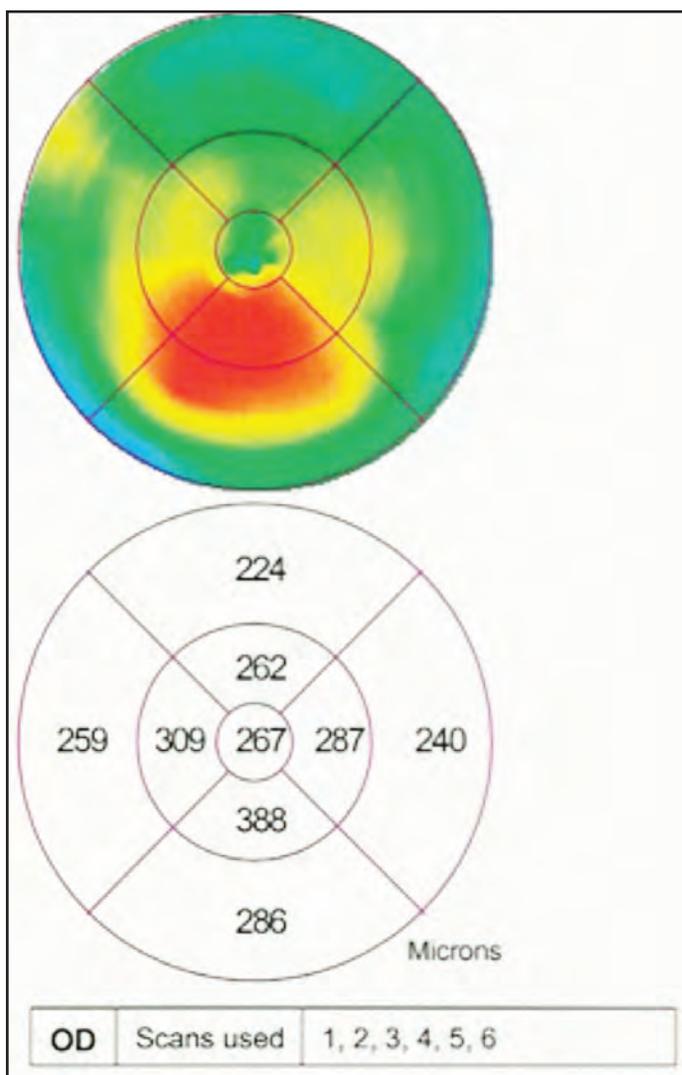


Figure 9: Focal DME. OCT map shows thickened area inferior to the fovea.

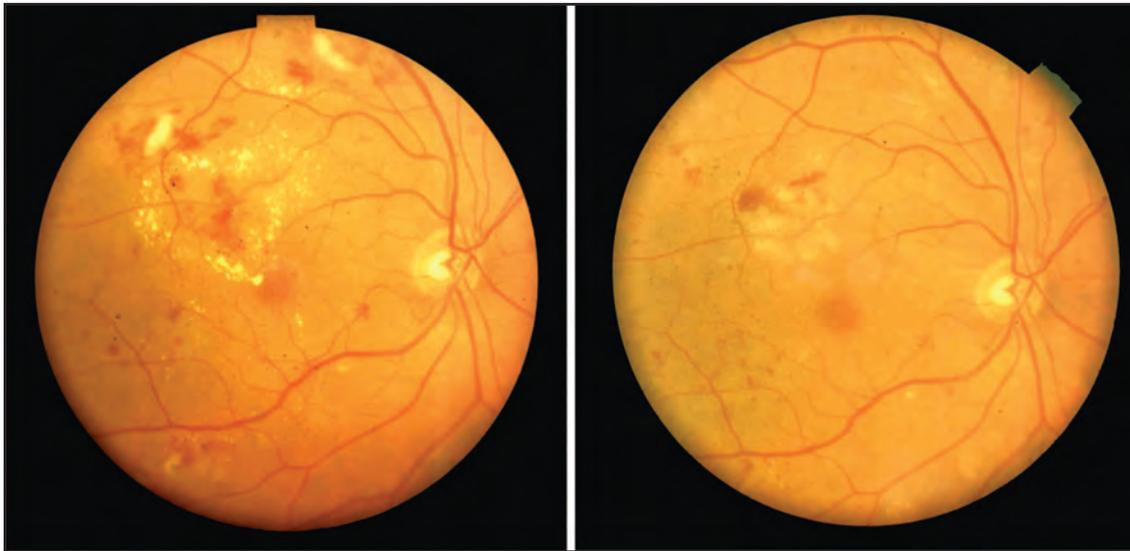


Figure 10: Focal DME before and after laser treatment.

Besides optimizing medical treatment, **laser** is the only accepted treatment for this type of DME. (Figure 10). If DME persists after the initial treatment, leaking lesions closer to the fovea may be treated up to 300 μm from the center of the fovea.

Diffuse DME. The macular area is diffusely thickened at the biomicroscopic examination. Lipid exudates are less prominent and usually do not show a circinate ring pattern.

Fluorescein angiography shows diffuse leakage of dye from the perifoveal capillaries

with a generalized breakdown of the blood-retina barrier (Figure 11). Eyes with 33% or less of fluorescein leakage associated with microaneurysm were classified as diffuse DME by the ETDRS.⁽⁸⁾ Fluorescein angiography may show cystoid spaces (Figure 12). OCT usually show increased macular thickness involving all quadrants, with loss of the foveal depression (Figure 13). A cystic pattern and/or a localized serous detachment of the macula may be demonstrated in some cases (Figure 11).

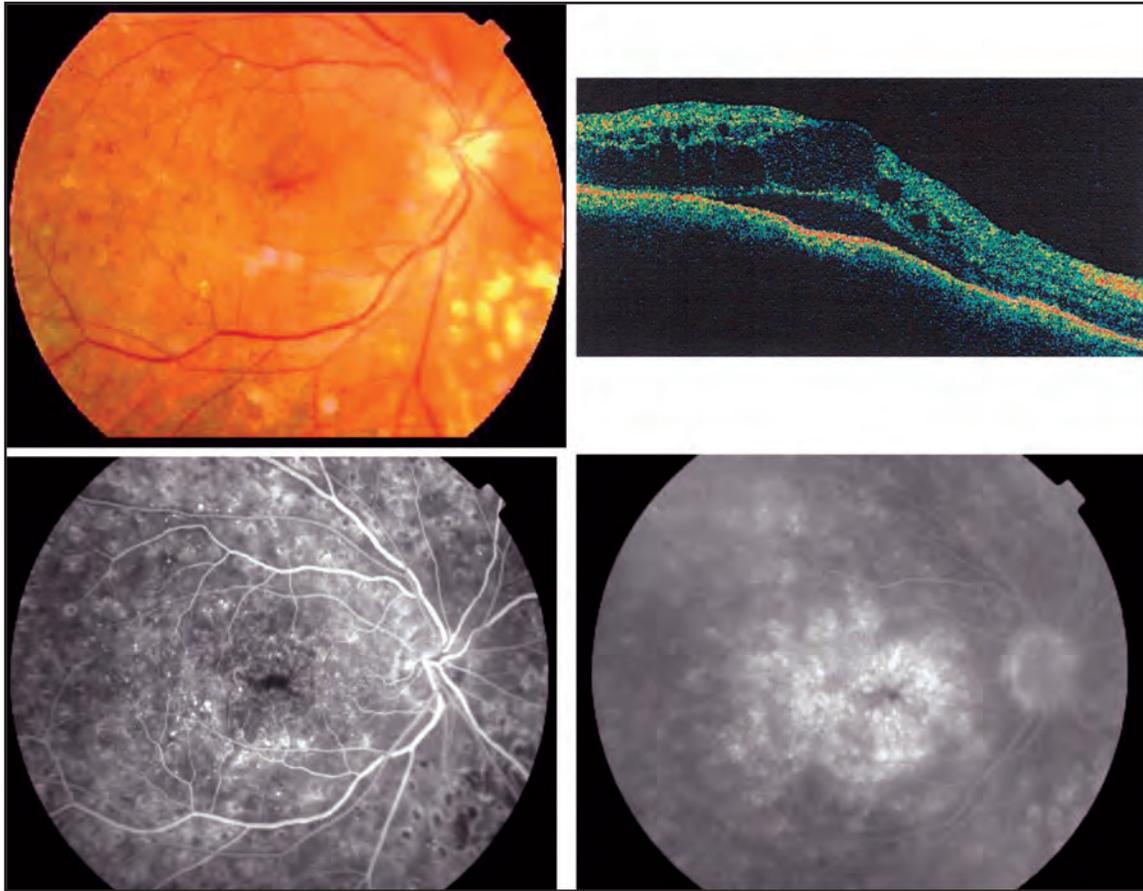


Figure 11: Diffuse DME. No significant lipid exudation. Diffuse thickening of the retina and subfoveal retinal detachment. Leakage of fluorescein in late phases of the angiogram.

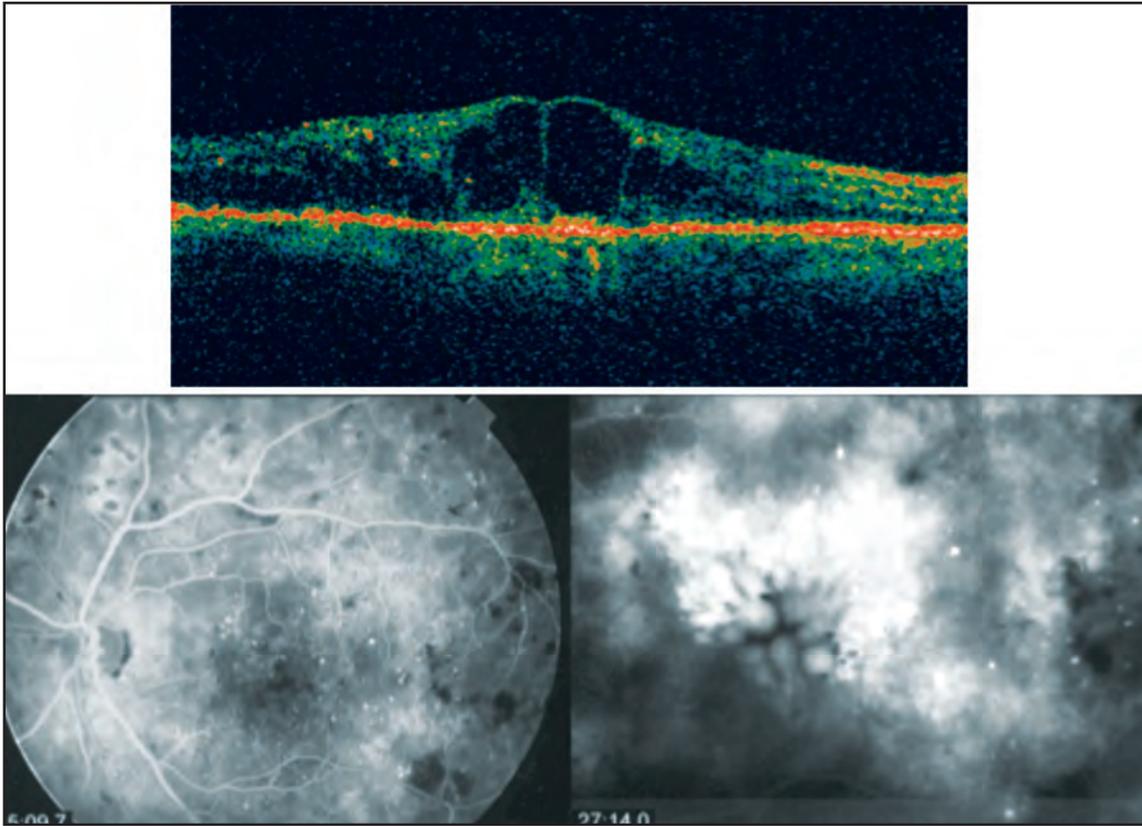


Figure 12: Cystoid diabetic macular edema.

Many authors have claimed that diffuse DME has a poorer prognosis and is refractory to laser photocoagulation in many cases, but the evidence to support these claims does not arise from prospective clinical trials. Grid pattern laser photocoagulation may be helpful in some patients, but we believe that applying laser to markedly thickened retina is difficult and hazardous, because the anatomic landmarks are lost and because a

higher power of the laser will be induced to obtain a visible burn.

If edema is greater than $390\ \mu\text{m}$, intravitreal triamcinolone or intravitreal anti VEGF therapy to help reduce edema prior to laser application holds theoretical benefit.⁽⁹⁾ If after one trial of laser, there is not significant improvement, a trial of intravitreal therapy may help, reducing macular edema for a more precise grid therapy.

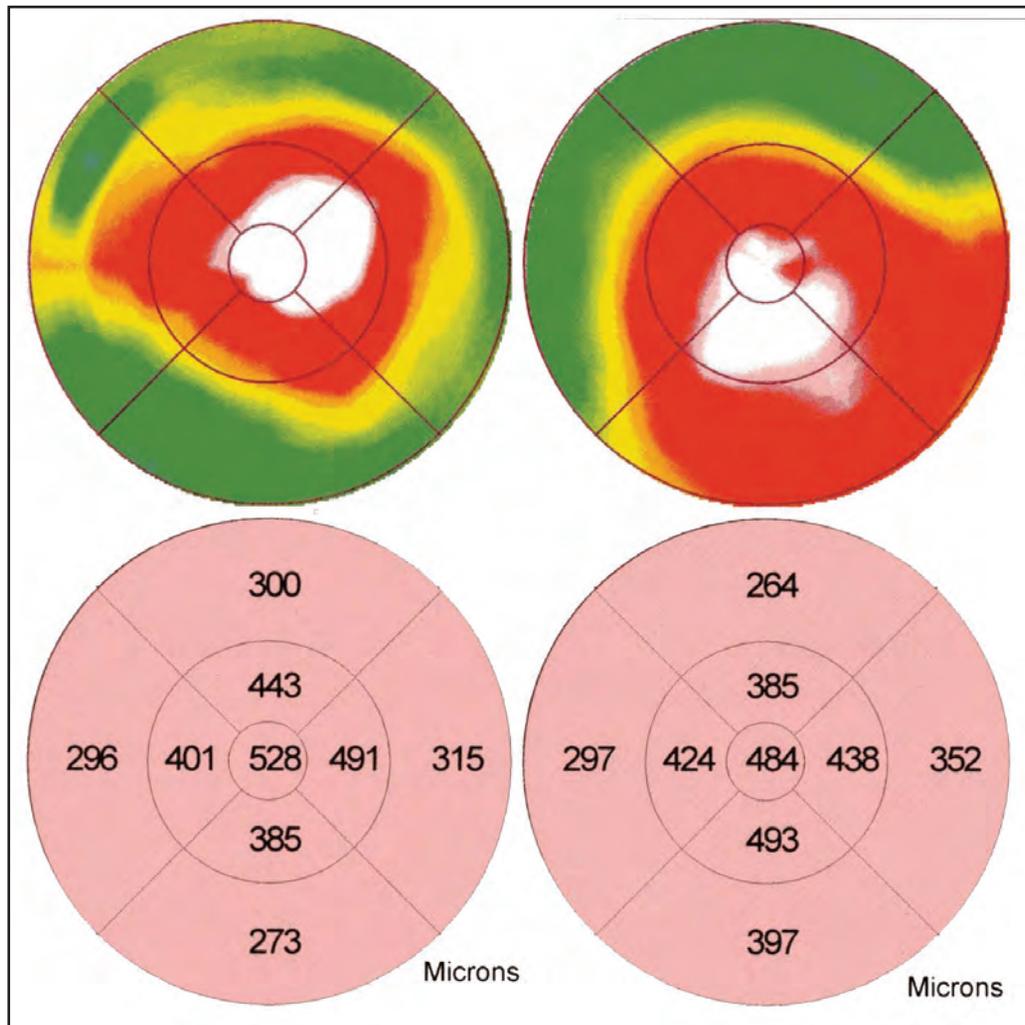


Figure 13: Diffuse macular edema. Increased macular thickness involving all quadrants.

LASER Treatment of DME

The burns should be placed 500-3000 μm from center of the macula in the first treatment. If retreatment is needed, burns could be placed 300-500 μm from center of macula.

The laser should darken or whiten the microaneurysm. For the grid treatment, mild, light burns of 100-200 μm are recommended, spaced one burn apart, 500 μm away from the center of the macula.

In eyes with severe non proliferative DR or early proliferative DR, the best strategy



is immediate focal photocoagulation with delayed scatter panretinal photocoagulation.

The Diabetic Retinopathy Clinical Research Network reported the two year results of a multicenter randomized clinical trial comparing intravitreal Triamcinolone and focal/grid laser for DME.⁽¹⁰⁾ The mean visual acuity at 2 years was better in the laser group, even though the short term visual results were better in the Triamcinolone injected eyes. However, half of the eyes in the photocoagulation group still had central retinal thickening at 2-years and approximately 20% of laser treated eyes worsened 10 letters or more from baseline.

The authors recognize that it is a role for better treatments in the future and combination treatments are currently being evaluated.

Pharmacologic Treatment of DME and Combination Treatments

Intravitreal corticosteroids and antiangiogenic agents have been used in treatment of DME. Many studies demonstrated significant anatomic and functional improvements following the intravitreal therapy. There are three major problems with this treatment modality:

1. They do not work in all cases.
2. The visual benefit is short lived and repeated injections are needed.

3. Intravitreal corticosteroids have substantial adverse effects.

Corticosteroids. Corticoids are potent antiangiogenic and antiinflammatory agents. A number of papers demonstrated significant visual improvement after repeated intravitreal injections of triamcinolone. Significant intraocular pressure elevation occurs in about 50% of patients and a high proportion of patients required cataract surgery.⁽¹¹⁾

The ideal dose of triamcinolone is not known. 4 mg is the most commonly used dose; higher doses (8 mg or more) may prolong the duration for the beneficial effect, but at adverse effects may be higher.

A single injection of 4 mg of triamcinolone usually causes an effective, but transitory reduction of macular edema, with maximum effect around 4 weeks, but the benefit is almost gone at 6 months (Figure 14).

Intravitreal corticosteroid implants have been developed, designed to release steroids into the vitreous for extended periods of time. Fluocinolone (Retisert, Bausch and Lomb) and dexametasone (Posurdex, Allergan) devices are undergoing clinical trials. Even though significant improvements in visual acuity have been reported, the side effects are significant (glaucoma and cataract surgery needed in a high proportion of cases) and limit widespread use in DME.

Anti-VEGF agents. Multiple studies have demonstrated that Pegnatinib, Bevacizumab and

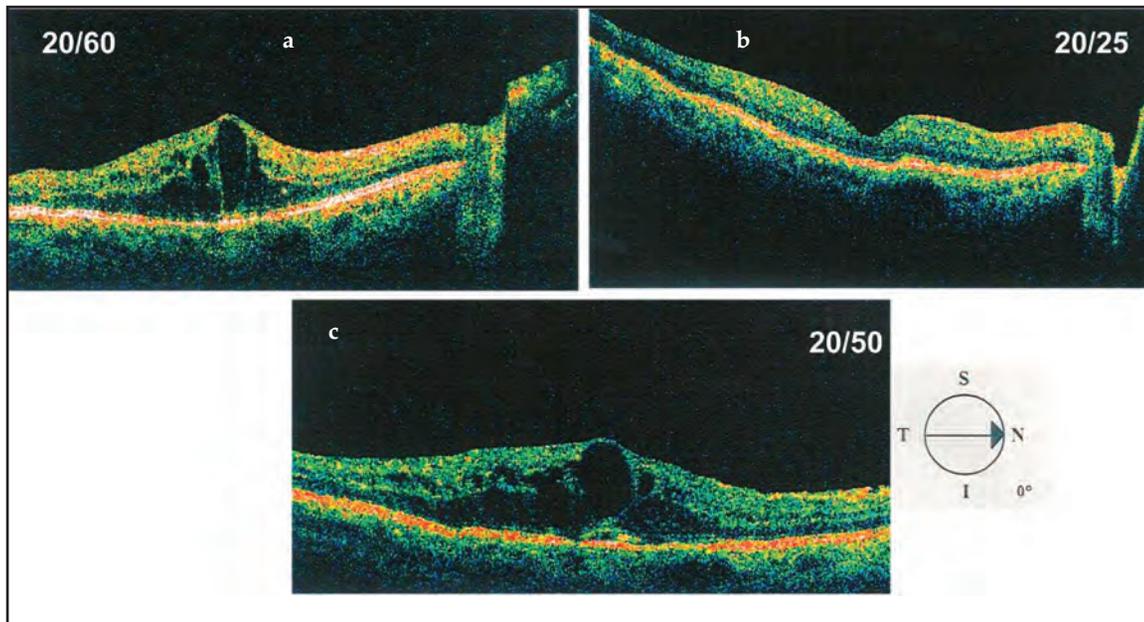


Figure 14: 54 year-old diabetic woman. Cystoid diffuse macular edema. a) baseline. b) one month after intravitreal Kenalog, 4 mg. c). 10 months after the injection.

Ranibizumab appear to be effective in improving vision and reducing macular thickness in the **short term** in primary treatment for DME or in refractory cases. Arevalo et al. have reported that primary intravitreal Bevacizumab for diffuse macular edema seems to provide stability or improvement of visual acuity at 24 months. The mean number of injections per eye was 5.0. However, 37 of 139 patients showed no change in visual acuity and 12 patients lost vision.⁽¹²⁾

Combination therapy. The main limitation of intravitreal pharmacologic therapy is the high recurrence rate of macular edema.

Repeated injections carry risks of complications and decreased efficacy. Kang et al.⁽¹³⁾ in randomized clinical demonstrated better visual and anatomic results with triamcinolone followed by macula grid laser compared with the triamcinolone only group. Lam study, suggested laser may prolong the effect of intravitreal triamcinolone⁽¹⁴⁾.

Several studies comparing combined therapy with laser are now being conducted. At this time, there is not solid scientific evidence to state that laser, performed at 3 weeks of the intravitreal injection, may prolong the effect of intravitreal agents.



A suggested algorithm for treatment of DME without vitreous traction.

1. Optimization of medical treatment.
2. Laser. Direct laser for leaking microaneurysm and grid treatment for areas of edematous retina with no defined focal leakage.
3. If there is a diffuse leakage with central thickness of $400\ \mu\text{m}$ or more we prefer to reduce retinal thickness with intravitreal therapy. We would start with an intravitreal Avastin injection, because of its fewer side effects. If no effect,

we would repeat the injection after one month. If there is no change in retinal thickness, we would proceed with a tramcinolone (Kenalog) 4 mg injection (Figures 15 and 16).

Corticosteroids are more potent agents for DME, given their anti-inflammatory capacity, in addition to their antiangiogenic effect.

4. Once a reduction in thickness is obtained, usually 3 weeks after the injection, laser, focal and grid is performed, under the guidance of a fresh angiogram.

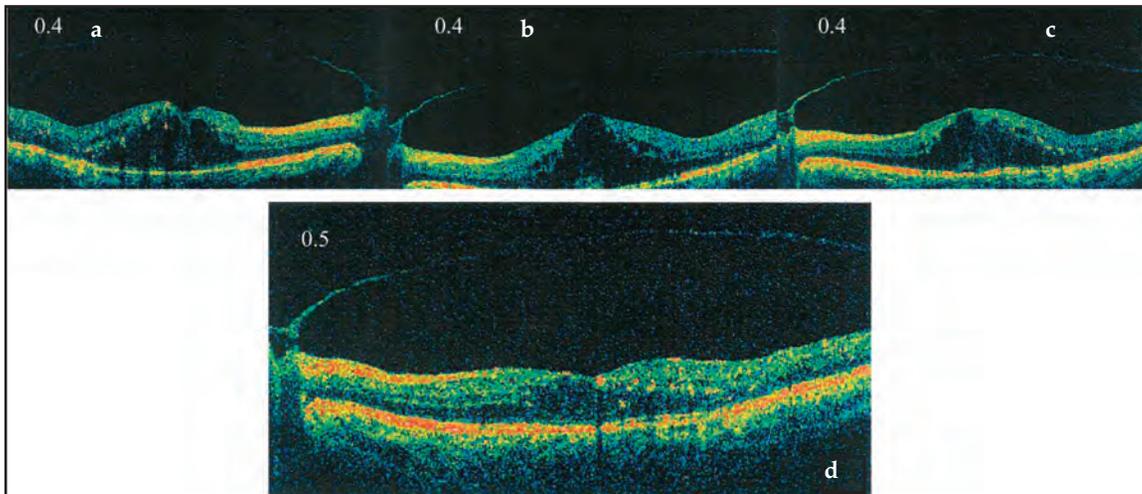


Figure 15: 53 year-old woman, diabetes 2 of 21 years duration, HbA1c 6.8%. Diffuse DME. a) pre Avastin. b) one month after first Avastin. c) one month after second Avastin. d) one month after intravitreal Kenalog.

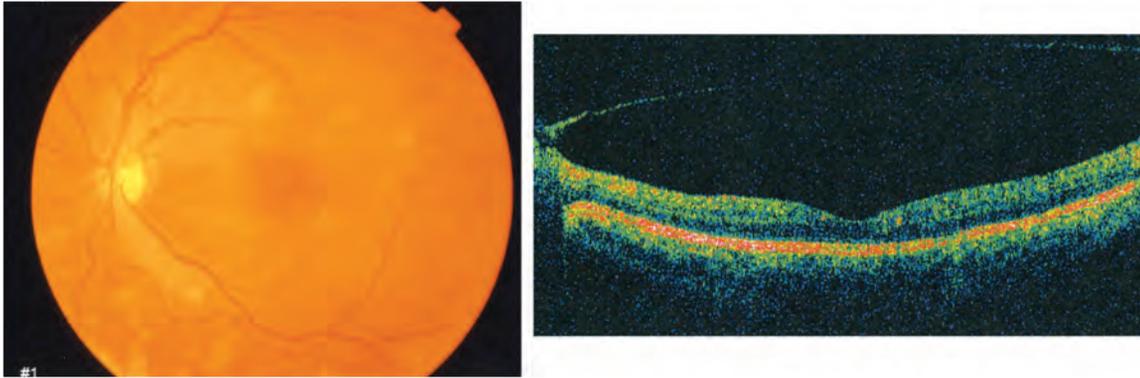


Figure 16: Same patient of Fig. 15. 18 months after Kenalog; 17 months after grid laser photocoagulation.

DME Associated with Posterior Hyaloidal Traction

Vitreomacular traction may cause diffuse macular edema in diabetic patients. The traction is not always clinically obvious at the biomicroscopic examination. The traction is easily visualized on OCT. Laser is ineffective and vitrectomy with stripping of the posterior hyaloid is indicated.

There is subset of patients with thickened, taut, glistening posterior hyaloid on clinical biomicroscopic examination with no posterior vitreous separation.⁽¹⁵⁾ OCT shows tangential traction and a shallow macular detachment

in some cases. Vitreoretinal surgery is often successful at restoring visual acuity.

Vitreous surgery for eyes unresponsive to laser or combined therapy and **without evidence of vitreomacular traction** is a matter of controversy. Results of several trials comparing pars plana vitrectomy versus laser are inconsistent. The role ILM peeling is not clear. Anatomic improvement may not parallel visual acuity improvement.

Vitrectomy should be considered as a last resort in eyes with severe DME, unresponsive to all therapies. Theoretically, eyes with an attached vitreous should have better surgical outcome, but this has not been demonstrated.

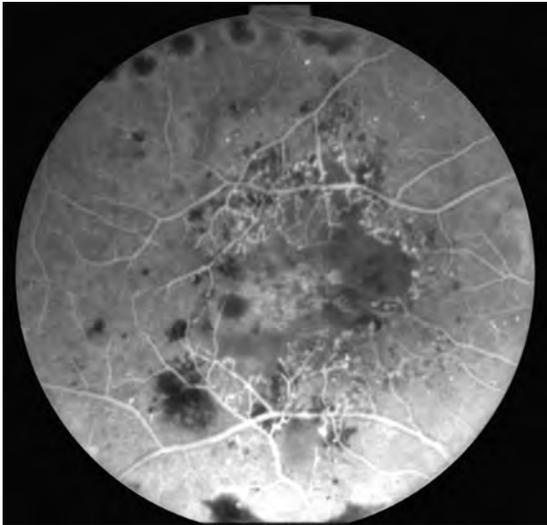
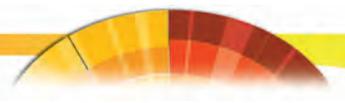


Figure 17: Ischemic DME.

DME with Retinal Ischemia

These eyes show an irregular enlargement of the FAZ (foveal avascular zone) with non perfusion of capillaries from the perifoveal net. In spite of capillary closure, dye leakage may be demonstrated in some eyes, probably

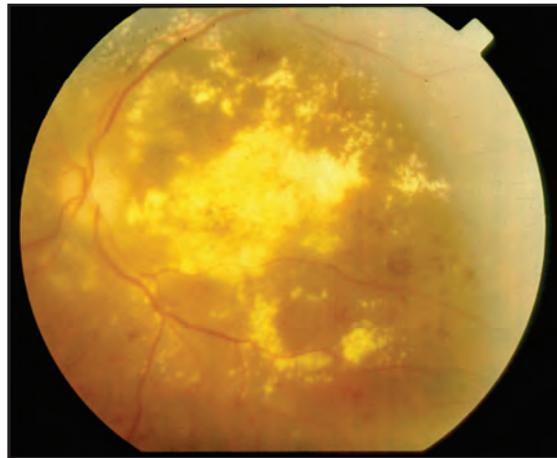


Figure 18: Long standing, massive lipid deposition at the macula.

derived from the retinal pigment epithelium (Figure 17). The visual outcome is usually poor. Even though some specialists do recommend laser treatment in these cases, we prefer to abstain. Laser treatment should be considered only if there is some demonstrable leakage on fluorescein angiography.

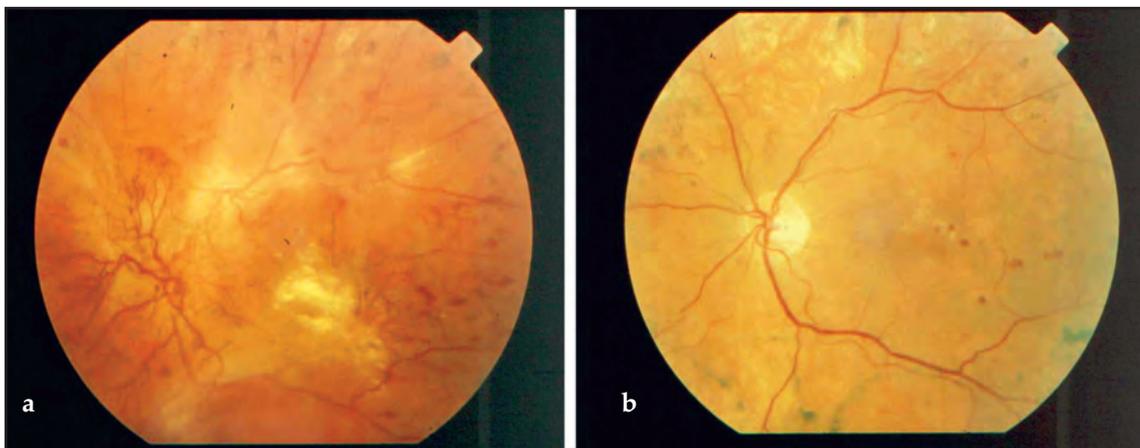


Figure 19: a) Active PDR in spite of a full panretinal laser photocoagulation. b) after vitreous surgery.



DME with Long Standing, Massive Lipid Deposition at the Macula

Those eyes show an elevated mound of hard exudates at the macula sometimes with highly reflective crystals (Figure 18). The prognosis for recovery of central vision is extremely poor, due to irreparable damage to the photoreceptors.

Diabetic Retinopathy: Indications for Vitrectomy

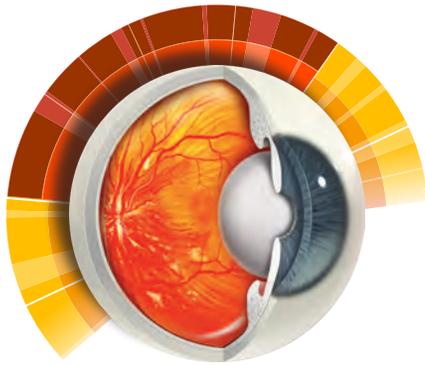
1. Severe, no clearing vitreous hemorrhage. Prompt vitrectomy and intraoperative photocoagulation is recommended in patients not previously treated with laser, in patients who have lost vision in the other eye, in Type 1 diabetic, and patients with rubeosis iridis.
2. Active, florid proliferative diabetic retinopathy (DPR) that persists despite a full laser panretinal photocoagulation (Figure 19).
3. If preretinal hemorrhage or a less severe vitreous hemorrhage do not allow an effective photocoagulation therapy.
4. Tractional retinal detachment that involves the macular area.
5. Combined traction-rhegmatogenous retinal detachment.
6. Patients with DME and significant vitreo-macular traction.

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12

Vitrectomy for Diabetic Retinopathy

JORGE I. CALZADA, MD

Introduction

Despite the availability of efficacious treatments for the management of diabetes, and the widespread use of laser photocoagulation in diabetic retinopathy, there are still a large number of patients that progress to advanced proliferative diabetic retinopathy. Modern vitreoretinal surgery techniques allow us to change the natural course of vision loss in advanced diabetic retinopathy, whether it may be proliferative diabetic retinopathy or macular edema. In the recent past, two developments have allowed us to consider earlier surgical intervention in progressive diabetic retinopathy:

1. Minimally invasive sutureless vitrectomy and
2. Pharmacological agents that block vascular endothelial growth factor (anti-VEGF). These tools have decreased the risk and discomfort associated to surgery while at the same time improving the surgical benefits. We must now view vitrectomy surgery

as another option in the management of diabetic retinopathy and not just as a last resort in patients facing blindness.

We will first review general concepts of patient selection and management in the different clinical scenarios that require vitrectomy in diabetes. In the latter part of this chapter we will discuss specific surgical techniques to be used in these pathologies.

Proliferative Diabetic Retinopathy

The two most common indications for vitrectomy surgery in the setting of proliferative diabetic retinopathy are vitreous hemorrhages and tractional retinal detachments.

a) Vitreous Hemorrhage

The Diabetic Retinopathy Vitrectomy Study (DRVS)¹ concluded that patients with vitreous hemorrhages that did not clear after



observation over the course of 6-12 months had better outcomes with vitrectomy than those observed without vitrectomy. As alluded to in the introduction, modern vitreoretinal surgery techniques allow us to recommend earlier vitrectomy than what the DRVS study concluded.

The goals of vitrectomy in diabetic vitreous hemorrhage are two fold:

1. To treat the underlying proliferative diabetic retinopathy and,
2. To clear the visual axis. Observation of a vitreous hemorrhage without treating the underlying disease can lead to unchecked progression of the retinopathy. Whenever a patient with diabetic vitreous hemorrhage is seen in the office, we first attempt to perform pan-retinal photocoagulation if the media permits it. Often younger patients will present with dense preretinal hemorrhages covering the posterior pole but with clear view of the retina beyond the vascular arcades (Figure 1). Since these hemorrhages may quickly disperse through the vitreous in the course of days to weeks, the opportunity provided by the clear view of the retina should allow adequate panretinal photocoagulation at the time of presentation.

When patients are seen with diffuse vitreous hemorrhages, two clinical questions should be answered:

1. Is the underlying retina attached? and,
2. Is proliferative diabetic retinopathy the cause of the vitreous hemorrhage? Binocular indirect ophthalmoscopy can often be per-



Figure 1: Acute subhyaloid hemorrhage in diabetic patient. These patients often present with acute central vision loss. The ophthalmologist should proceed with panretinal photocoagulation within the week of diagnosis. These subhyaloid hemorrhages often progress to diffuse vitreous hemorrhages, which preclude adequate laser therapy. Early laser therapy allows treatment of the underlying retinopathy before the media opacities impede it.

formed through dense vitreous hemorrhages to determine if the retina is attached or not, even if no subtle retinal details are seen. Often the view of the preequatorial retina is better than the view of the posterior pole, and that may be enough to determine the status of retinal attachment. If the view simply does not permit ophthalmoscopy, B-scan ultrasonography should be performed to determine retinal status. A patient with an underlying retinal detachment with vitreous hemorrhage requires early vitrectomy instead of observation.

The clinician should always think of the differential diagnosis of vitreous hemorrhage, even in diabetic patients. If the fellow eye



does not have proliferative retinopathy, one should consider the possibility of a different etiology for the vitreous hemorrhage. Whereas some causes of vitreous hemorrhages can be managed by clinical observation with the same timeline as diabetes (eg vein occlusions or sickle cell retinopathy), the possibility of a retinal tear with vitreous hemorrhage may push us into recommending a diagnostic and therapeutic vitrectomy within 1-2 weeks to prevent the development of a rhegmatogenous retinal detachment.

If proliferative diabetic retinopathy is the cause of the vitreous hemorrhage, and the media opacity prevents laser photocoagulation, a new option for therapy is intravitreal anti-VEGF therapy (ie: bevacizumab or ranibizumab). Anti-VEGF will cause regression of the diabetic neovascularization in most patients in the course of 1-2 weeks.² This medication is a competitive antagonist of VEGF, and as such it does not stop the synthesis of VEGF. In other words, even if anti-VEGF allows early regression of the neovascularization, the neovascularization will recur if no further treatment to the underlying disease is undertaken. Recurrence of neovascularization after anti-VEGF therapy occurs approximately 3-4 months post treatment. During this period, the clinician must either perform panretinal photocoagulation in the office or proceed to vitrectomy and endolaser if the hemorrhage does not clear adequately for office laser treatment. Anti-VEGF, therefore, allows the surgeon to decide on the merits of vitrectomy based on the patient's vision loss, and its impact to the patient's daily life. Given the success of sutureless vitrectomy, most younger and active patients agree with vitrectomy after an observation period of 4-6 weeks.

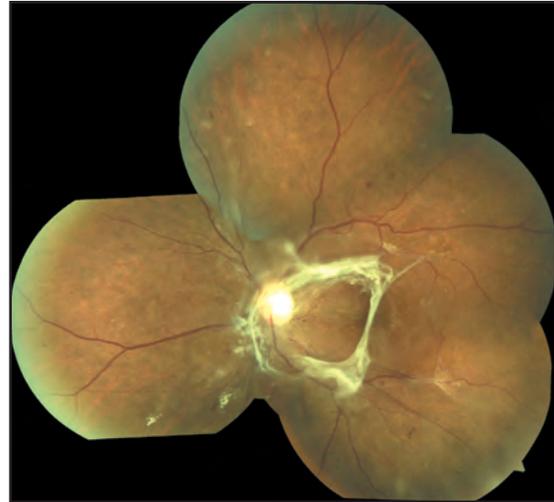


Figure 2: Preretinal fibrous contraction in diabetes. The “sphincter” configuration of the preretinal membrane is typical of proliferative diabetic retinopathy. Although the retina is attached, the contraction of the membranes has produced retinal traction with macular striae. Scissors dissection of the epiretinal membrane can release the traction on the fovea.

b) Tractional Retinal Detachments

Tractional retinal detachments constitute one of the most interesting and surgically challenging pathologies in vitreoretinal surgery. Diabetic tractional retinal detachments occur secondary to contractions of vitreous and of epiretinal fibrovascular proliferation in proliferative diabetic retinopathy (Figure 2). Neovascularization usually starts at the optic nerve head and courses along the vascular arcades, often forming a complete ring around the macula after meeting in the temporal raphe. Regression and consequent contraction

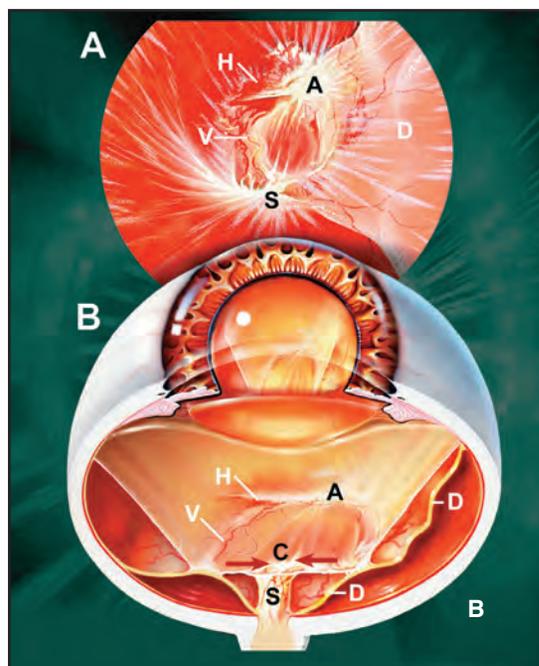


Figure 3 a-b: **a)** Severe fibrovascular proliferation in proliferative diabetic retinopathy. Note the active vascular component of the preretinal membranes. The ophthalmologist can expect contraction of the membranes with panretinal photocoagulation or intravitreal bevacizumab treatment. The patient should understand that his vision may worsen early in the course of treatment. The ophthalmologist should follow closely the patient following treatment, and early vitrectomy with scissors delamination of the epiretinal tissue should be performed in case of progression to traction retinal detachment. **b)** Severe, Advanced Proliferative Diabetic Retinopathy, Very High-Risk. Artistic rendition of severe, advanced proliferative diabetic retinopathy at very high risk. (A) Shows a fundus view of a severe case of proliferative diabetic retinopathy. There are preretinal hemorrhages (H) in several locations. Note the extensive active fibrovascular proliferation causing a traction detachment (D) nasally due to traction from the fibrovascular tissue (A) on the retina. There is also active fibrovascular proliferation along the retinal vessel arcade (V) with detachment of the macular area. Note the active fibrovascular stalk (S) which obscures the optic nerve. (B) Shows the same eye with surgeon's view as seen through the pupil, and accompanying cross section view of the tissue pathology. Note hemorrhage (H), traction (arrows) of the posterior hyaloid (C), traction detachment of the retina (D), and active fibrovascular stalk (S) on the optic nerve. (B- Art from Jaypee-Highlights Medical Publishers).



Figure 4: Severe fibrovascular proliferation in proliferative diabetic retinopathy. Clinical scenario is similar to figure 3. Note the communication of the fibrovascular tissue between the superior to the inferior vascular arcade. This patient has a very high risk of progression to traction retinal detachment.

of the active neovascularizations leads to two different tractional vectors on the retina: a) Tangential traction along the retinal surface and b) Antero-posterior vitreous traction on the pathological vitreous attachments on the epiretinal fibrovascular tissue. Surgical repair of diabetic traction retinal detachments requires release of all tractional vectors on the retinal surface (Figures 3 a-b, 4).

Indications for vitrectomy surgery in diabetic tractional retinal detachments are detachment of the fovea with central vision loss and extrafoveal retinal detachments with functionally significant scotomas. We will discuss the technical issues regarding tractional retinal detachment repair later in this chapter.

Non-proliferative Diabetic Retinopathy: Macular Edema

a) Vitreo-Macular Traction Syndrome

The abnormal vitreoretinal interphase in diabetics is often the cause of diabetic macular edema. Optical coherence tomography has allowed us to evaluate the anatomy and relationship of the fovea and vitreous in detail, and can show obvious antero-posterior traction on the fovea and often a localized foveal detachment³ (Figures 5, 6 and 7). Diabetic macular edema can now be understood as having three possible pathogenic causes: a) Focal leakage from macular

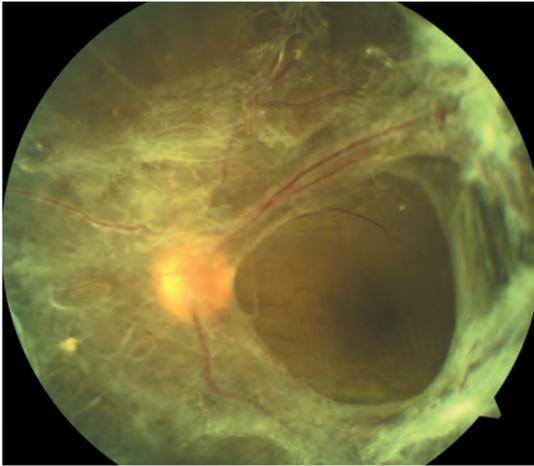


Figure 5: Diabetic traction retinal detachment. The macular area appears detached secondary to preretinal traction and contraction of the fibrovascular “sphincter” that is typical of proliferative diabetic retinopathy.

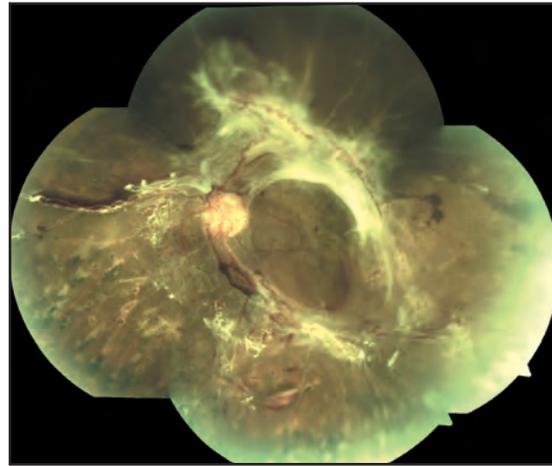


Figure 7: Chronic diabetic traction retinal detachment. Despite peripheral laser, there is persistent vascular activity of the neovascular tissue. The retina appears atrophic and translucent from chronic traction and ischemia. The retinal vessels beyond the arcades appear occluded. This patient has a poor visual prognosis even with anatomic reattachment of the retina with vitrectomy surgery.

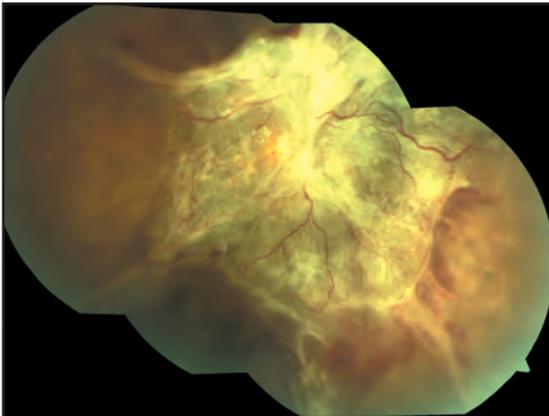


Figure 6: Severe diabetic traction retinal detachment. Massive preretinal proliferation precludes identification of anatomic landmarks. Radial retinal folds extend towards the equator of the globe. Careful observation of the vasculature of the preretinal tissue allows identification of retinal vessels and neovascular proliferative vessels: Retinal vessels exhibit dichotomous branching, whereas abnormal neovessels branch in irregular fronds. Presence of small neovessels indicate activity of the proliferative process.

microaneurysms (best managed with focal laser photocoagulation), b) Diffuse macular edema secondary to breakdown of the macular capillary blood-retinal barrier⁴ (which is the most difficult form to treat) and c) Tractional macular edema from vitreomacular traction or epiretinal membrane. A particular patient may have components of all three of these mechanisms, which need to be specifically addressed to achieve resolution of the macular edema (Figures 8 a-b and 9). The recent introduction of high resolution OCT allows greater ability to evaluate the vitreo-macular anatomy.

In the presence of foveal traction, release of the traction is often necessary for resolution of the macular edema. To achieve this, we recommend sutureless 25 G vitrectomy with

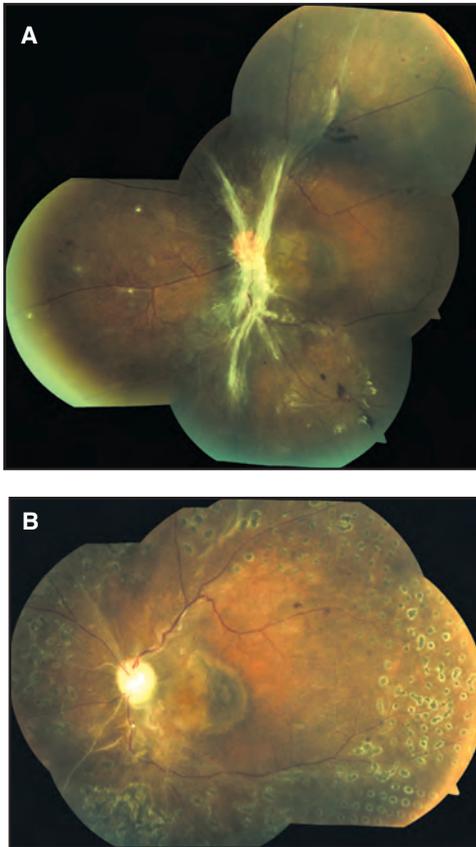


Figure 8 a-b: a) Macular traction detachment in type 1 diabetes. 25 year old patient with uncontrolled diabetes. The posterior vitreous was attached temporal to the optic nerve, but remained attached nasal and inferior to the optic nerve. Note the configuration of the neovascular vessels nasal to the nerve, which appear flat against the retinal surface, since the posterior hyaloid is still attached. The papillo-macular bundle is incorporated into the fibrovascular tissue at the optic nerve head, which has caused a localized detachment of the macula with 20/400 vision. b) Postoperative result two weeks following vitrectomy with scissors delamination of epiretinal membranes of the patient in figure 8a. This patient was initially treated with intravitreal bevacizumab and panretinal photocoagulation. Vitrectomy was later performed by the author and all the fibrovascular tissue was successfully removed without complications. After only two weeks following surgery, there is significant improvement in the retinal anatomy, but there is still a small amount of submacular fluid that hasn't been reabsorbed after the retinal traction was removed. The macula reattached completely one month after vitrectomy, with final visual acuity of 20/100.

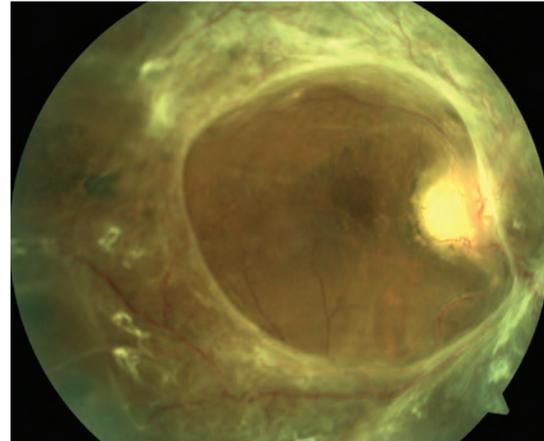


Figure 9: Typical diabetic traction retinal detachment. The configuration of the preretinal fibrovascular tissue follows the growth of neovascularization from the nerve head along the temporal arcades, meeting at the horizontal raphe temporal to the macula. In addition to this obvious component of traction along the retinal surface, the surgeon must recognize and surgically relieve the antero-posterior vector of traction caused by the posterior hyaloid attachment immediately peripheral to the preretinal tissue, which often cannot be discerned until the time of surgery. The sharp circular outline along the preretinal tissue in this picture is likely caused by the premacular posterior vitreous cortex attachment to the neovessels. This premacular vitreous often forms a taut "trampoline" above the retina, and should also be removed at the time of surgery.



complete removal of the posterior hyaloid. Great care must be taken not to create a iatrogenic macular hole while removing foveal traction. To this effect, the surgeon often has to carefully peel all the perifoveal epiretinal membrane or posterior hyaloid, paying attention to the tractional forces on the fovea to determine the direction of highest mechanical resistance, and finish peeling the fovea in this same direction, avoiding unroofing a foveal cyst and creating a secondary lamellar macular hole.

b) Persistent Diffuse Diabetic Macular Edema

Non-tractional macular edema, particularly that associated to diffuse breakdown of the blood-retinal barrier in the macula, may be recalcitrant and resistant to treatment. The medical and laser management of macular edema is not in the scope of this chapter. It will suffice to enumerate different treatment strategies that should be considered before recommending vitrectomy for the management of these patients:

1. Focal and macular grid photocoagulation.
2. Optimization of systemic disease status (hypertension, hyperglycemia, congestive heart failure, proteinuria with hypoalbuminemia, obstructive sleep apnea, etc.).
3. Cessation of systemic medications that may exacerbate macular edema (eg. Rosiglitazone or Niacin).
4. Periocular or intravitreal steroids.
5. Intravitreal anti-VEGF agents. In the absence of foveal traction, vitrectomy should

not be performed until the previous strategies have been considered.

Peeling of the macular internal limiting membrane has been shown to be efficacious in the management of persistent diabetic macular edema in the absence of foveal traction.⁵ The rationale for this procedure involved removal of any potential non-obvious retinal traction, and decompartmentalization of macular tissue. This could allow macular interstitial fluid to be dissolved in the vitreous cavity and to provide a larger volume of distribution of VEGF with decreased concentrations in the macula.

The work done by Holekamp has demonstrated that the vitreous gel acts as an oxygen sink, and that vitrectomy increases oxygen levels in the vitreous cavity.⁶ The vitreous likely consumes oxygen through ascorbic acid. The removal of the vitreous gel is associated to significant increase in the partial pressure of oxygen in the vitreous cavity and particularly on the retinal surface. The increased oxygen pressure in post-vitrectomy eyes is directly responsible for the accelerated progression of nuclear sclerotic cataracts after vitrectomy surgery. On the other hand, the increased vitreous oxygenation may have the positive effect of supplying much needed oxygen to the retina in ischemic retinopathies.

No large controlled studies have been performed to determine the most appropriate surgical procedure for persistent diabetic macular edema. It is important to mention that the only common denominator in all surgical strategies proposed for diabetic macular edema is core vitrectomy. Current



surgical strategies other than core vitrectomy include vitrectomy with removal of the posterior hyaloid or vitrectomy with internal limiting membrane peeling. It is difficult to objectively determine at this time if core vitrectomy without any membrane peeling is as effective as vitrectomy with peeling of the ILM or posterior hyaloid. We recommend vitrectomy with posterior hyaloidectomy. Intraoperative triamcinolone can be utilized to demonstrate the presence of the posterior hyaloid attachment, and to guarantee its complete removal. Atraumatic internal limiting membrane peeling can be attempted in most patients. If the ILM peeling is technically difficult, we see no present benefit to risking retinal damage if the vitrectomy and posterior hyaloid have been successfully performed. We anxiously await large controlled surgical studies of vitrectomy for macular edema to further refine these recommendations.

A caveat that the physician must remember and inform the patient with diffuse diabetic macular edema is that not uncommonly the visual acuity doesn't improve after successful treatment and resolution of the macular edema. The limiting factor may be macular ischemia from diabetic microvascular damage of the perifoveal capillaries. In addition, there may be recurrence of the macular edema months after resolution with vitrectomy.

Technical Issues

a) 25 G Sutureless Vitrectomy

Advances in vitreoretinal technology and instrumentation have provided the surgeon the ability to perform sutureless transcon-

junctival vitrectomy. Sutureless vitrectomy has many significant benefits over standard 20 gauge vitrectomy. The preservation of the ocular surface and the conjunctival integrity significantly decreases postoperative patient discomfort and pain, as well as hastens visual recovery. Glaucoma is a frequent comorbidity, and sutureless vitrectomy doesn't scar the conjunctiva in case of a future trabeculectomy and can avoid completely a previous glaucoma surgery site, decreasing the likelihood of failure or leak from a filtration or seton surgery. The fluidics and anterior location of the port in the vitreous cutter allow safer vitrectomy and permits epiretinal membrane delamination with the cutter itself. At the time of this writing, the main controversies regarding sutureless vitrectomy are whether to use 23 gauge or 25 gauge vitrectomy for sutureless vitrectomy. Many surgeons believe that sutureless vitrectomy is only amenable for simple surgical cases and that complex cases require 20 gauge instrumentation. We use 25 gauge vitrectomy for all our cases, simple and complex.

As mentioned in the discussion of vitreous hemorrhages, preoperative intravitreal anti-VEGF has become a tool in the surgical management of proliferative diabetic retinopathy. Anti-VEGF causes regression of retinal neovascularization within one to two weeks, and decreases postoperative vitreous hemorrhage, which otherwise can occur in up to a third of patients following vitrectomy for proliferative diabetic retinopathy. In patients with large active neovascularizations, worsening of retinal traction can occur after anti-VEGF therapy.⁷ Due to this, we proceed with the intravitreal anti-VEGF injection four

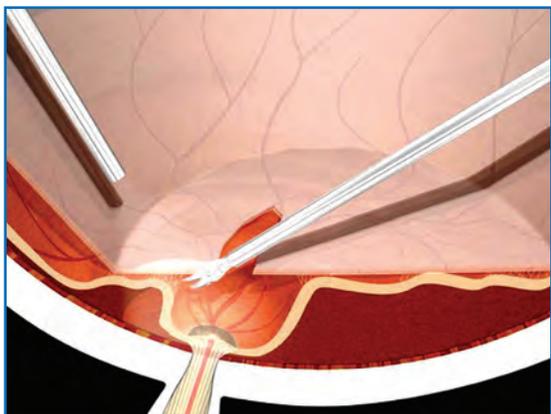


Figure 10: Technique for scissors delamination of epimacular membranes. This picture demonstrates various important anatomic considerations that should guide the surgical dissection of diabetic traction retinal detachments. 1. Epiretinal membranes often have multiple discrete attachment points to the retina that can be cut with scissors in the correct dissection plane. 2. The posterior vitreous cortex usually remains attached at the sites of neovascular proliferation. 3. Vitreous contraction occurs in two planes: a peripheral cone that attaches to the vitreous base, and a horizontal plane above the macula. The surgeon must remove all vectors of traction for complete reattachment of the retina. (Courtesy of *Vitreous Microsurgery* book, Fourth Edition, by Steve Charles, Jorge Calzada and Byron Wood. L).

to seven days prior to vitrectomy, instead of waiting for complete contraction of the retinal membranes after the anti-VEGF injection. In addition, at the end of diabetic vitrectomy surgery, we inject anti-VEGF into the vitreous cavity, to maintain the inhibition of VEGF during the early postoperative period.

In the presence of dense vitreous hemorrhage that precludes visualization of the retinal surface, great care must be taken to avoid creating an inadvertent retinal tear with the vitreous cutter. We recommend performing a

central vitrectomy and “tunneling” vertically towards the optic nerve or nasal retina, rather than extending the core vitrectomy peripherally without retinal visibility. Once the optic nerve is recognized the surrounding retinal anatomy will become easier to identify, and the core vitrectomy can be extended peripherally (Figure 10).

Following core vitrectomy, attention is directed to the posterior vitreous cortex. In diabetic traction retinal detachments, there is usually a persistent vitreous attachment along the arcades or other areas of retinal neovascularization. The vitreous can then take the configuration of a truncated cone as the peripheral vitreous detaches from the retinal surface, but maintains attachments at the vitreous base and vascular arcades. The vitreous cutter is used to transect the posterior hyaloid 360 degrees along the surface of the cone, resolving the anteroposterior traction on the retina. Intraoperative intravitreal triamcinolone can be used for vitreous visualization during surgery. Although not necessary in all patients, triamcinolone does facilitate completeness of the truncation of the posterior hyaloid.

b) Posterior Hyaloid Dissection

The posterior hyaloid is the common site of pathology that has to be addressed during diabetic vitrectomy. In proliferative diabetic retinopathy, the hyaloid is the substrate for growth of retinal neovascularization and for creation of retinal traction. The surgical dissection of epiretinal tissue (discussed below) removes the posterior hyaloid simultaneously.



Diabetics often present with “decortication” or separation of layers of the posterior hyaloid during posterior vitreal detachment. A surgeon may incorrectly believe that the posterior hyaloid has been completely removed, and not identify a persistent layer of vitreous cortex on the surface of the retina. Intraoperative triamcinolone greatly facilitates the identification of the anatomy of the posterior hyaloid. The surgeon may choose to engage the posterior hyaloid overlying the optic nerve with the vitreous cutter in suction mode or use intraocular forceps in the macular area to peel the hyaloid.

Identification of areas of retinal neovascularization (NV) that have persistent vitreous attachment is important, since these areas are often responsible for postoperative vitreous hemorrhages or retinal traction. These NV-vitreous attachment sites should be removed with the vitreous cutter or intraocular scissors to decrease these postoperative problems.

c) Epiretinal Membrane Dissection

Epiretinal proliferation in diabetic traction retinal detachment usually has the conformation of plaques of fibrovascular tissue attached to the underlying retina by multiple discrete point vascular stalks. Each individual attachment site requires to be cut to safely remove the epiretinal tissue. If the attachment sites are not severed, but pulled on (by forceps instead of scissors, for example), there is a high risk of creating a retinal tear. Scissors delamination is the technique where the scissor blades are used parallel to the retinal

surface and closed between the epiretinal tissue and the underlying retina, cutting the attachment sites. Scissors segmentation is the technique where the scissor blades are used perpendicular to the retinal surface to transect epiretinal tissue. Segmentation can be used to gain access to a specific epiretinal dissection plane for subsequent delamination, or can be used to relieve traction without further delamination.

Delamination and segmentation with the vitreous cutter has been made possible with the newer high speed cutters and with small gauge vitrectomy, since 25 and 23 G cutters have the port closer to the tip of the instrument than older 20 G cutters. Currently, after truncating the peripheral cone of posterior hyaloid, we use the cutter to perform access segmentation of the posterior epiretinal tissue. The cutter can also be used to delaminate plaques of dense epiretinal tissue without damaging the underlying retina. Fast cutting rates and low suction should be used to perform these difficult technique.

The most appropriate site for initiation of epiretinal tissue dissection is at or near the optic nerve, whenever possible. Whereas all other retinal areas may be detached and potentially mobile, the optic nerve is the only structure of the fundus that is not, facilitating dissection at its surface. In addition, once access to the epiretinal dissection space is achieved at the optic nerve, further centrifugal dissection towards the arcades is made significantly easier and safer. Dr. Steve Charles coined the term “inside-out delamination” to illustrate the notion of



initiation of the epiretinal tissue dissection at the epicenter (the safest location), and proceeding outwards rather than attempting to find the most peripheral edge of epiretinal tissue (usually overlying an area of retinal thinning) and proceeding inward.

Great care must be used when delaminating to avoid creating iatrogenic retinal tears. Many surgeons recommend bimanual dissection for traction retinal detachment dissection. To do this, a broad chandelier illumination system must be utilized, either through the infusion cannula (in 20 G surgery) or through a fourth entry port (in 25 G systems). This allows the surgeon to use a forceps in one hand and scissors in the other, facilitating delamination techniques. We do not regularly use chandelier illumination or bimanual techniques, since we are able to perform scissors delamination with the standard three port techniques, using the endoilluminator in one hand and the scissors or vitreous cutter in the active hand.

Although removal of all surface traction is optimal, the surgeon should remember that the goal of surgery is reattachment of the posterior retina and macula (Figures 11a-e). This becomes an issue when peripheral and nasal epiretinal tissue is encountered. Dissection over peripheral atrophic retina is very prone to creation of iatrogenic retinal tears. It is always best to leave peripheral traction present without retinal tears than attempt total peripheral dissection, creating peripheral retinal tears and further complicating the management of the retinal detachment.

We do not recommend intentional creation of a retinotomy for subretinal fluid drainage in traction retinal detachment surgery. Surgical removal of the retinal traction will lead to postoperative retinal reattachment through pumping of the subretinal fluid by the retinal pigment epithelial cells. Intentional retinotomies require air, gas or silicone oil tamponade, postoperative head positioning and increase the risk of postoperative proliferation and cataract formation.

d) Management of Retinal Tears

Iatrogenic retinal tears occur frequently in traction retinal detachment surgery. Surgeon's skill, experience and technique can minimize the creation of retinal tears, but the fact remains that retinal tears will be encountered. In addition to iatrogenic retinal tears, tractional cystic retinoschisis or full thickness retinal holes can be often found spontaneously after long standing retinal traction. The first step in management of intraoperative retinal tears is early detection of the tear, to stop further enlargement of the tear. Once the tear is detected, all retinal traction surrounding the tear must be resolved. If there is any traction acting on the tear, the edges of the tear will not settle properly over the retinal pigment epithelium postoperatively, and a rhegmatogenous retinal detachment will eventually occur. Subretinal fluid drainage with simultaneous fluid-air exchange can then be performed through the retinal tear. If all retinal traction has been removed, the retina should become reattached under air. If the retina doesn't reattach completely, that is clear

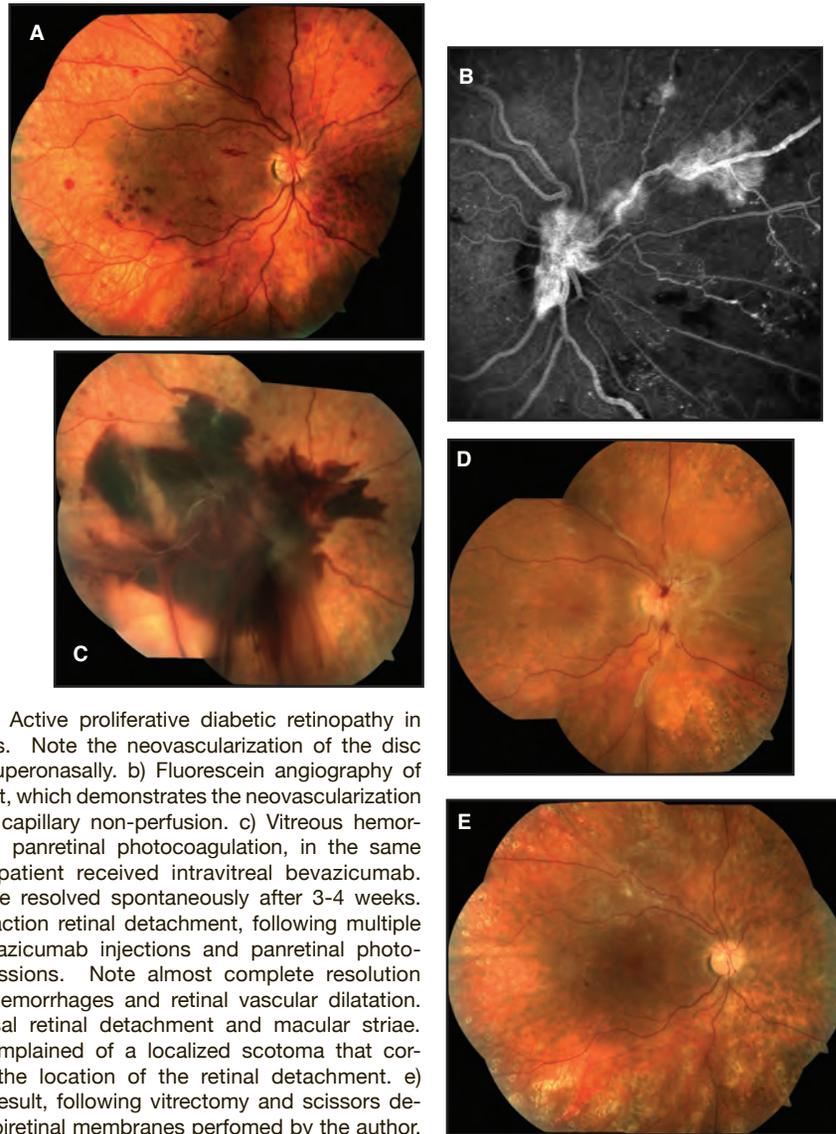


Figure 11 a-e: Active proliferative diabetic retinopathy in type 1 diabetes. Note the neovascularization of the disc that extends superonasally. b) Fluorescein angiography of the same patient, which demonstrates the neovascularization and peripheral capillary non-perfusion. c) Vitreous hemorrhage following panretinal photocoagulation, in the same patient. The patient received intravitreal bevacizumab. The hemorrhage resolved spontaneously after 3-4 weeks. d) Localized traction retinal detachment, following multiple intravitreal bevacizumab injections and panretinal photocoagulation sessions. Note almost complete resolution of intraretinal hemorrhages and retinal vascular dilatation. There is a nasal retinal detachment and macular striae. The patient complained of a localized scotoma that corresponded to the location of the retinal detachment. e) Postoperative result, following vitrectomy and scissors delamination of epiretinal membranes performed by the author. Note complete resolution of the retinal detachment and foveal striae. The diabetic retinopathy appears quiescent. The final visual acuity was 20/20, with resolution of the scotoma related to the retinal detachment.



indication of persistent retinal traction and need for further dissection. The surgeon may choose to operate under air or to return to a fluid-filled eye for continuation of the retinal dissection. Once the retina is reattached, endolaser retinopexy should be performed around all retinal tears, in addition to the panretinal photocoagulation. We commonly use SF₆ gas for postoperative surface tension management. In the event that the retinal traction cannot be safely removed completely, we utilize silicone oil tamponade.

e) Management of Intraoperative Hemorrhage

With the advent of preoperative intravitreal anti-VEGF, significant intraoperative hemorrhage has decreased significantly. In the event that such hemorrhages occur, the surgeon must be familiar with techniques to deal with this problem. It is inappropriate to simply stop surgery without addressing the retinal pathology because of intraoperative hemorrhage. The first step in the management of hemorrhage is the elevation of intraocular pressure above the retinal perfusion pressure. This is the equivalent of applying direct pressure on a general surgery wound. Once the bleeding has been stopped, intraocular cautery or direct laser photocoagulation can be utilized for hemostasis. Fluid-air exchange can also be done to let a blood clot to form over the area of hemorrhage, allowing visualization of all other retinal areas. Intraocular thrombin or other procoagulants have been used with some success,⁸ although we do not find much use for these medications. In the event that persistent hemorrhage precludes

finishing the removal of all retinal traction or adequate laser retinopexy around retinal tears, it is preferred to fill the vitreous cavity with silicone oil at the end of the procedure and plan for reoperation two to four weeks postoperatively than let untreated tears progress to rhegmatogenous retinal detachment in the postoperative period.

f) Endophotocoagulation

In the case of macular edema, the endolaser probe can be used to perform focal photocoagulation to microaneurysms in the macular area. We do not recommend performing grid endolaser photocoagulation, since this technique ablates potentially viable retina and doesn't treat the underlying pathology of the macular edema.

Endopanretinal photocoagulation should be performed in cases with proliferative diabetic retinopathy. Several authorities recommend panretinal photocoagulation extending to the ora serrata in cases of severe proliferative diabetic retinopathy. We have not found this to be necessary, and, on the other hand, it increases the risk of peripheral retinal tears, damage to the lens in phakic patients, and increases surgical time, which is an important consideration in diabetics that often have coexisting systemic morbidities.

g) Management of the Lens

Removal of the lens during vitrectomy for diabetic retinopathy can increase postoperative complications, so cataract surgery should be decided cautiously. If the view to the retina



is sufficient for achievement of the goals of vitrectomy surgery, then it is best to leave the lens alone, even in the presence of a mild to moderate cataract. It is always safer to perform standard phacoemulsification with intraocular lens implantation as a separate procedure after recovery from the vitrectomy surgery than attempt to combine them in a single operation.

If a cataract is dense enough to preclude adequate vitrectomy then cataract surgery is in order. In these cases we perform standard phacoemulsification through a clear corneal incision and place a foldable acrylic lens in the capsular bag. Regarding intraocular lens selection, silicone IOLs should be avoided, given the possibility of silicone oil tamponade after the vitrectomy. There is not enough data at this time to recommend multifocal IOLs in the setting of diabetic vitrectomies, so we currently prefer simple monofocal IOLs to provide optimal visual input to these diseased maculas. Great care should be taken during the cataract surgery to maintain constant anterior chamber depth and avoid touching the iris with the surgical instruments, since this would increase the likelihood of intraoperative miosis and postoperative inflammation. If the pupil is small or if there are significant posterior synechiae that require synechiolysis, it is best to use iris hooks or a similar pupillary expansion device during surgery. Once placed, these devices can be left in place until the vitrectomy surgery has been finished. While most well constructed cataract surgery wounds are water tight without

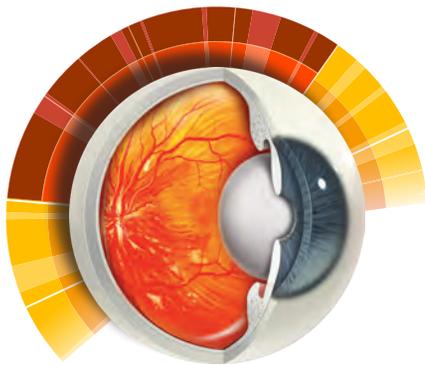
suturing, postoperative hypotony secondary to the sclerotomies can deform the corneal wound and cause it to leak. Due to this, we prefer to place a single 10-0 nylon suture on the corneal wound after the cataract surgery portion of the procedure. If there are any difficulties with placing a posterior chamber IOL in the bag or even in the ciliary sulcus, it is best to leave the eye aphakic than to hastily place an anterior chamber IOL. Secondary IOL placement can be performed in the future. The surgeon should always keep in mind that the primary goal of the surgery is to fix the retinal pathology, and that cataract surgery and IOL implantation should not interfere with this primary goal.

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13

Pars Plana Vitrectomy in the Management of Diabetic Macular Edema

MARIA H. BERROCAL, MD

Diabetic macular edema can be caused by a number of different pathologies. These include focal edema caused by microaneurysms, diffuse macular edema caused by incompetence of the capillary wall, thickened posterior hyaloid, vitreomacular traction and epiretinal membranes. Argon laser photocoagulation has been the mainstay of treatment as evidenced by the EDTRS for clinically significant macular edema secondary to capillary leakage.^{1,2} With the advent of optical coherence tomography (OCT) for diagnostic evaluation, a tractional component of macular edema has been disclosed in some cases. This tractional etiology has shown to be responsive to management by vitrectomy. Pars plana vitrectomy has shown to be beneficial in the management of macular edema associated to macular traction from epiretinal membranes or a thickened posterior hyaloid, vitreomacular traction syndrome and pre-retinal hemorrhage. Nevertheless, the treatment of diffuse macu-

lar edema without an associated tractional component has been controversial. Treatment modalities of photocoagulation, vitrectomy, and intravitreal pharmacotherapy have been attempted with varying results.

Etiologies of Diabetic Macular Edema

Diabetic macular edema secondary to a tractional component can be divided into several subgroups depending on the underlying pathology. These include traction from a thickened premacular posterior hyaloid membrane, diffuse edema from a partially attached premacular posterior hyaloid without a thickened membrane or traction from an epiretinal membrane in an eye with a posterior vitreous detachment (PVD). The widespread use of the optical coherence tomography (OCT)



has increased the accuracy of the diagnosis of the underlying vitreoretinal pathologies in these cases. It has made it possible for the clinician not only to determine if there is a tractional component but also to assess the degree of retinal edema present. Small, shallow localized macular detachments can be easily visualized with this modality.

Vitreomacular Traction

This diagnosis was very difficult to make prior to the advent of OCT. Previously, gliosis

observed by contact lens slit lamp biomicroscopy as well as diffuse leakage by fluorescein angiography were used for diagnosis. Nevertheless, the gold standard for diagnosis is the OCT. In these eyes, vitreomacular traction on the fovea causes diffuse edema, and/or foveal detachment. These eyes have shown positive responses to management with pars plana vitrectomy to remove the hyaloid. The edema and localized foveal detachment resolves slowly over time with slow improvement of visual acuity (Figures 1 and 2).

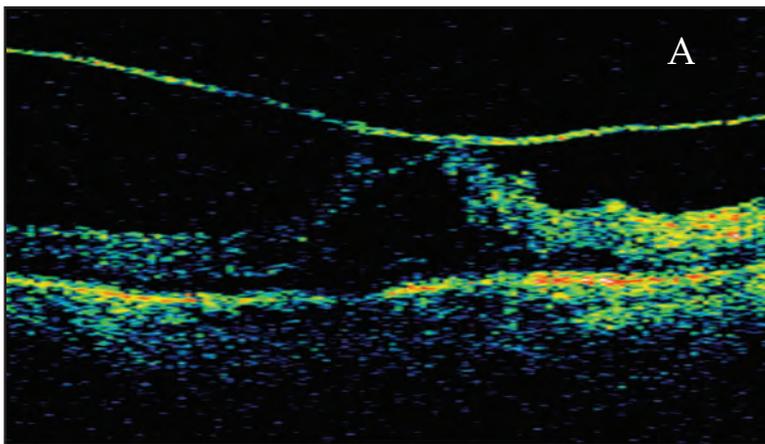
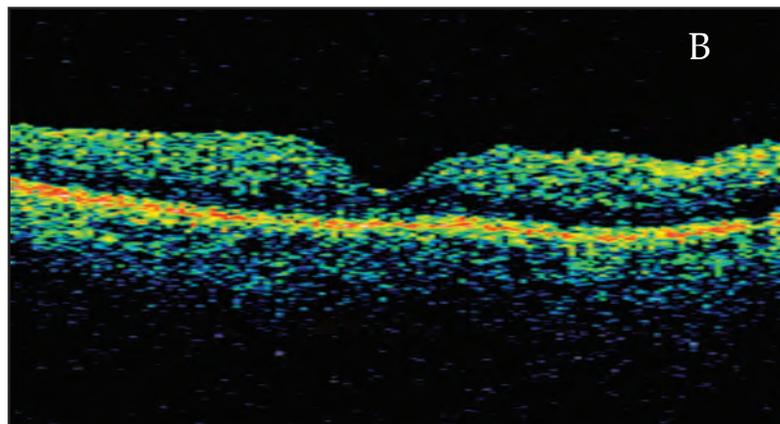


Figure 1a-b: a) Posterior hyaloids exerting traction on foveal region Va 20/400. b) Resolved traction and edema 6 months post vitrectomy Va 20/50.



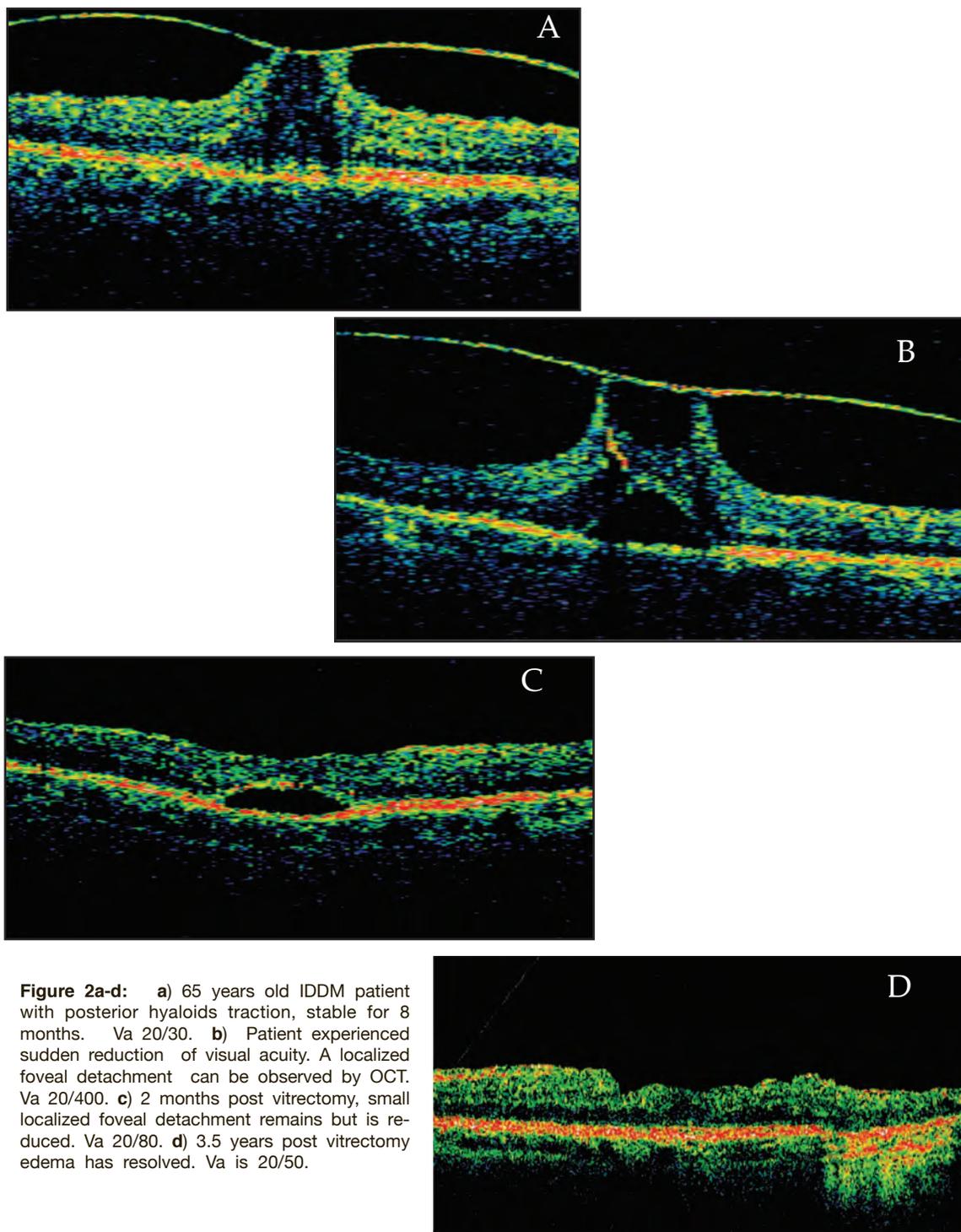


Figure 2a-d: a) 65 years old IDDM patient with posterior hyaloids traction, stable for 8 months. Va 20/30. b) Patient experienced sudden reduction of visual acuity. A localized foveal detachment can be observed by OCT. Va 20/400. c) 2 months post vitrectomy, small localized foveal detachment remains but is reduced. Va 20/80. d) 3.5 years post vitrectomy edema has resolved. Va is 20/50.



In eyes with a partially attached premacular posterior hyaloid or vitreomacular traction syndrome, the tractional forces are antero-posterior (Figure 1). These cases can develop cystoid macular edema changes and a localized foveal neurosensory detachment which can cause severe, acute visual acuity loss. They can also develop lamellar holes (Figure 3). In 1992 Lewis et al reported promising results in eyes with diabetic macular edema from traction from a taut premacular posterior hyaloids membrane.³ In these eyes fluorescein angiography (FA) demonstrated

deep retinal diffuse leakage. The pathogenesis of this leakage was speculated to be at the level of the retinal pigment epithelium (RPE) from traction on the fovea and tangential tractional forces causing a shallow macular detachment. In this series of 10 eyes visual acuity improved in 90% at 6 months. All eyes showed glistening on biomicroscopy which can be confused with an epiretinal membrane, but no tortuosity was seen (Figure 4). This study was done prior to the use of OCT and biomicroscopy and fluorescein angiography were utilized for diagnosis.

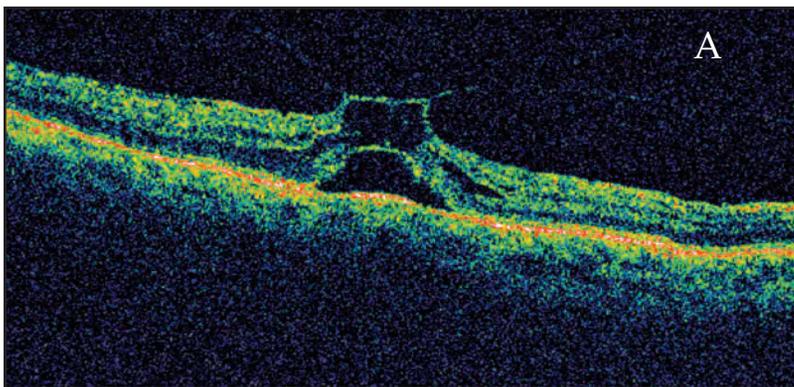
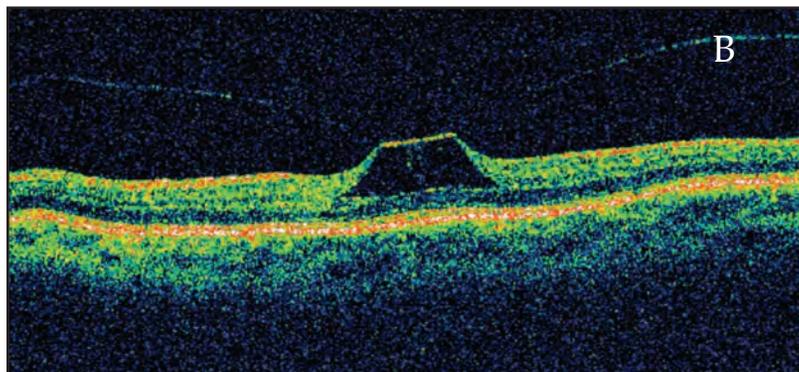


Figure 3 a-b: a) Vitreomacular traction causing a localized foveal detachment and a lamellar hole. Right eye Va 20/100. b) Vitreomacular traction causing a lamellar hole. Left eye Va 20/25.



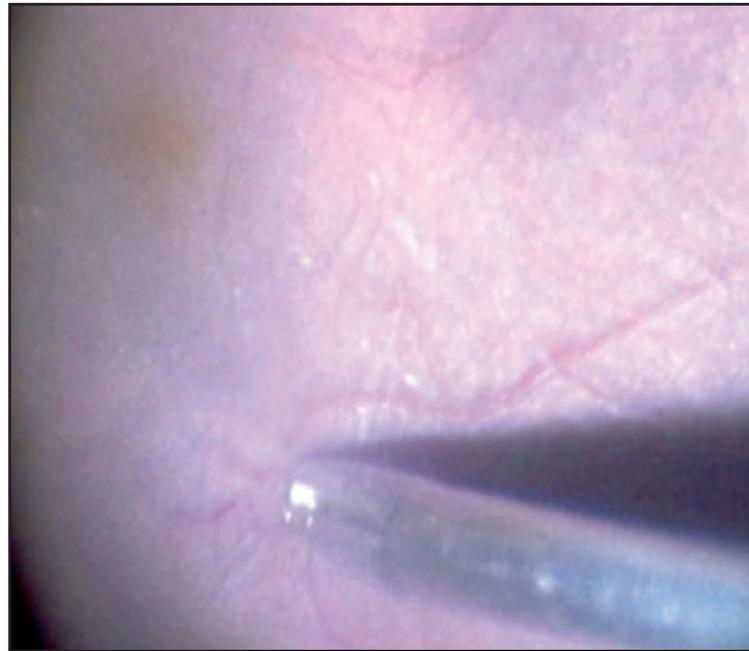


Figure 4: Thickened hyaloids with sheen on retinal surface.

Vitrectomy for diffuse macular edema associated to an attached premacular posterior hyaloid without a thickened hyaloid membrane has been shown to improve visual acuity outcomes. Tachi et al reported promising results with vitrectomy in these cases.⁴ They postulated that the edema in these cases can be the result of significant extravasation from retinal vessels secondary to vitreous traction as well as from breakdown of the inner and outer blood-retina barrier. These eyes showed vitreous attachment but no visible hyaloid membrane. In this series, macular edema re-

solved in 67% of eyes at 6 months and 98% at 1 year with visual acuity improvement in 53% of eyes at 1 year.

Diffuse Macular Edema

Diffuse macular edema occurs from generalized incompetence of the capillary vascular wall. Its treatment has been controversial and difficult. In the past, grid photocoagulation has been utilized with modest results.⁵ Intravitreal triamcinolone has been compared to



photocoagulation in the DRCR.net. Intravitreal triamcinolone, followed by photocoagulation has been utilized, as well as ranizumab and bevacizumab injections. Pars plana vitrectomy with or without ERM and /or ILM peeling has been utilized with varying results.

Aydin et al evaluated pharmacological management of diffuse macular edema. They concluded that intravitreal triamcinolone produced better visual results than grid-laser alone. IVTA followed by laser was better than IVTA alone or at the same time as the laser treatment.⁶

Frase-Bell et al demonstrated that the VEGF inhibitors bevacizumab and ranizumab both resulted in a significant reduction in foveal thickness in eyes with diffuse edema.⁷ Similar results were demonstrated with bevacizumab by Kook et al and Arevalo et al. Kook et al showed no change in visual acuity at 6 months but an improvement of 5 lines on average at 12 months.⁸ Arevalo et al showed an improvement in visual acuity at 24 months in 52% of eyes treated with bevacizumab.⁹

Beck et al reported the DRCR. net 3 year results of a comparison between grid laser photocoagulation and ICTA using 1 and 4 mg of IVTA.¹⁰ Between 2 and 3 years all eyes improved, but by 3 years the laser group had gained 5 letters of visual acuity whereas the IVTA group showed no gain in visual acuity. The incidence of cataract progression was 31% in the laser group, 46% in the 1mg IVTA, and 83% in the 4mg group. Intraocular pressure

increased 10mg in 4% of lasered eyes, 18% of 1mg IVTA and 33% 4mg IVTA.

Results of Vitrectomy for Diffuse Macular Edema

Park et al reported 66% of eyes showing resolution of edema at 12 weeks post vitrectomy.¹¹ He postulated that in diffuse edema macular flow is augmented and vitrectomy causes reduction and flow and thus of edema.

Kumagai et al reported results of 486 eyes treated with vitrectomy and posterior hyaloids removal.¹² 36% of these eyes had ILM removal also. At 5 years post-op 52.7% improved, 31.3% remained unchanged and 16% worsened visual acuity. Complications in this series included NVG in 3.9%, vitreous hemorrhage in 2.1%, increased hard exudates in the fovea in 4.3%.

In a series by Yamamoto et al of 65 eyes with diffuse diabetic macular edema, 45% improved, 49% remained unchanged and 6% decreased visual acuity. They found that central macular thickness fluctuated and decreased up to 4 months post vitrectomy.¹³

Whether or not to remove the internal limiting membrane (ILM) in cases of diffuse macular edema remains controversial. Hartley et al reported on 24 eyes treated with vitrectomy and ILM peeling for these eyes.¹⁴



In this series 25% improved, 54% remained unchanged and 21% decreased visual acuity. Despite the modest improvement in visual acuity, retinal thickness in the foveal region by OCT was reduced.

Others have attempted concomitant treatment. Figueroa et al treated 42 eyes with pars plana vitrectomy, ILM peeling and or intravitreal triamcinolone.¹⁵ They noted a reduction in macular thickness by OCT from 1-6 months only. Visual acuity only improved in 12%, remained unchanged in 76% and decreased in 12%. They concluded that the procedure produced a temporary reduction in foveal thickness but no anatomical or functional benefit at one year post vitrectomy.

Diagnosis

Patients with diabetic macular edema typically present with decreased visual acuity and metamorphopsia, although a central scotoma can occur in cases of foveal detachment or a large foveal exudate. The decreased vision is usually gradual but can be acute in cases in which a localized macular detachment is present. Slit lamp biomicroscopy reveals retinal thickening which can be accompanied by hard exudates or a glistening sheen. Fluorescein angiography reveals localized or diffuse leakage and areas of capillary non-perfusion. OCT is very useful as it demonstrates the degree of edema, cystoid components, epiretinal membranes, thickened hyaloids, and tractional components. It also shows areas of localized

retinal detachment. And any interfase pathology.

Management

Focal areas of edema caused by microaneurisms are best treated by focal laser photocoagulation. In cases of diffuse macular edema it is important to determine if it is caused solely by vascular leakage or if there is a tractional component associated. Cases without a tractional component can have a response when treated with triamcinolone, VEGF inhibitors or vitrectomy, but results are variable. Eyes with a tractional component, are best managed by vitrectomy

Vitrectomy can be performed with a three port system in either 20, 23 or 25g, although the recent trend is towards microincision surgery with sutureless techniques. Preoperative OCT is imperative to determine if the hyaloids is attached, if a thickened hyaloids is present and if there is a localized retinal detachment or a lamellar hole. Fluorescein angiography is important to determine if significant capillary loss or ischemia is present. These eyes can have a poor visual outcome.

It can be useful to use intraoperative triamcinolone to stain the vitreous and the hyaloid and facilitate their removal. The partially detached hyaloids can be incised with a pick or blade and peeled. A thickened hyaloids can be lifted with a pick or peeled directly with forceps. Tripan blue can also be



used to stain ERM's or a thickened hyaloids to aid in visualization. In cases of significant traction or if a localized foveal retinal detachment is present an air/fluid exchange can be done to help resolve the detachment. Often, in cases of foveal detachment, after the traction is removed, the detachment can take months to resolve gradually. Eyes with significant traction can benefit from a longer acting gas and prone positioning. Post vitrectomy, the edema tends to resolve gradually.

Complications

Complications include iatrogenic retinal breaks and retinal detachment, iatrogenic macular hole, vitreous hemorrhage, RPE damage in the foveal region, cataract progression, phototoxicity, and endophthalmitis.

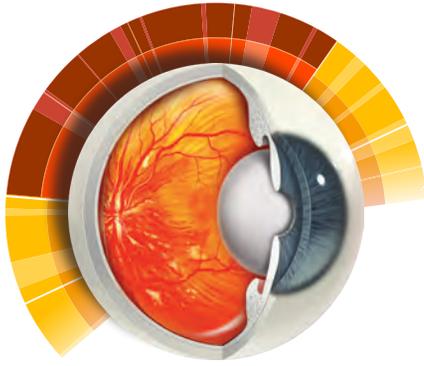
Conclusions

The benefit of pars plana vitrectomy for the management of diabetic macular edema in which there is a tractional or mechanical component has been established. Nevertheless the management of diffuse diabetic macular edema without a tractional component remains controversial. Published reports have shown conflicting results with a large variability. This can be explained by the multifactorial aspects of diabetic macular edema. Duration of edema, degree of associated capillary dropout and ischemia, degree of inflammation, quantity of hard exudates in the foveal region and the metabolic state and control of the patient are all variables that can affect visual outcomes in these eyes.

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14

The Vitreous in Diabetes

PROF. PATRICK C. P. HO, MD

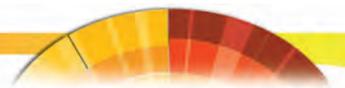
The vitreous is the largest tissue in the human eye and is responsible for numerous ophthalmologic diseases. Its pre-programmed degeneration from early childhood through adult life leads to vitreous detachment and subsequent retinal problems, many of which are sight threatening. This chapter discusses the vitreous anatomy, its subsequent degeneration in diabetic patients leading to tractional retinal detachments and macular edema.

The vitreous gel in non-diabetic eyes generally goes through aging changes consisting of lacunae formation, syneresis and posterior separation. It has been observed that in diabetic eyes without retinopathy, there seems to be a lower incidence of lacunae formation compared to non-diabetic eyes of a similar age group. And among the diabetics, eyes with non-proliferative retinopathy are observed to have a higher incidence of posterior vitreous separation than eyes without clinical evidence

of diabetic retinopathy in the same age group. Therefore, it appears that the presence, and the activity of the diabetic retinopathy promote vitreous changes, and thus posterior vitreous separation.

In adults, the vitreous body volume is approximately 4 mL, which is 80% of the globe. The content of the vitreous is 99% water, and the remaining 1% is mostly composed of collagen and hyaluronic acid. Additionally, there are a few other soluble components such as ions, proteins, and trace cells. These components account for the gelatinous but clear nature of the vitreous.

The vitreous is avascular and inelastic. Pathological mechanisms of vitreous hemorrhage can include hemorrhage from diseased retina, traumatic insult, and/or spread of hemorrhage into the retina and vitreous from fibrous intraocular traction.



Vitreous Shrinkage

Vitreous fluorophotometric studies have demonstrated that in diabetic eyes, even without clinically detectable retinopathy, there occurs a breakdown in the blood-vitreous barrier. It is further suggested that leakage of blood constituents into the vitreous gel as a result of this barrier breakdown leads to shrinkage of the vitreous gel and therefore posterior vitreous separation with, and frequently without, lacunae formation and syneresis. In diabetic eyes with active retinopathy, retinal neovascularities also leak into the vitreous gel and further promote vitreous shrinkage and contraction.

Vitreoretinal Adhesions

In response to retinal ischemia in a diabetic eye, new retinal vessels proliferate. These proliferations are typically located in the surface of the retina and insinuate between the inner retinal surface and the vitreous posterior cortical surface. When fibrocytes are subsequently laid down and proliferate, the new proliferation gradually turns from a neovascular nature to fibrovascular and finally

into a fibrous proliferation in the form of membranes which bind the vitreous cortex with the retinal surface. These proliferations constitute points or areas of vitreoretinal adhesions of various tenacity which, depending on the nature of the adhesion (mainly vascular-cortical, fibrovascular-cortical, or fibro-cortical) and also depending on the chronicity of the adhesion, result in complications.

The new vessels leak blood constituents into the cortical vitreous which subsequent undergoes shrinkage and contraction, separating from the posterior retinal surface at places where there are no firm vitreoretinal adhesion and a partial posterior vitreous separation results.

Some years ago, I have conducted a pilot study of looking at the status of the vitreous in eyes of diabetic patients at first presentation to my retinal clinic before any treatments were given. Those eyes which were found to have proliferative diabetic changes at initial presentation, 64% had a partial posterior vitreous separation and only 2% had a complete separation, whereas in eyes in non-proliferative changes initially, 7% had partial separation and 22% had complete posterior vitreous separation (Table 1).

Table 1
Initial Vitreous Findings in Patients With Diabetic Retinopathy

Vitreous separation:	None	Partial	Complete
Non-proliferative cases	71	7	22 (%)
Proliferative cases	34	64	2 (%)



Partial Posterior Vitreous Separation

Clinically, the vitreous could best be observed using a +78 preset lens and a slit lamp biomicroscope which can produce a thin but strong slit beam. The preset lens facilitates observation of the vitreous cortical movement on eye excursions. It is also important for the observer to become dark adapted before vitreous examination. Turning off all the lights in the examination room and the observer closing his eyes for 30 seconds before the examination would help. Ensuring that the

patient's pupil is widely dilated would also facilitate the examination although unfortunately, in many diabetic eyes, the pupils do not dilate well.

A partial posterior vitreous separation is frequently accompanied in a diabetic eye with a dense posterior hyaloid surface which can be traced posteriorly to the area of vitreo retinal adhesion (Figure 1). The hyaloid surface is thickened, tight and taut, and demonstrates very little movement on ocular excursion. The vitreous cortical gel is dense, hazy and may contain particles, bleaches blood, or even fresh hemorrhage.

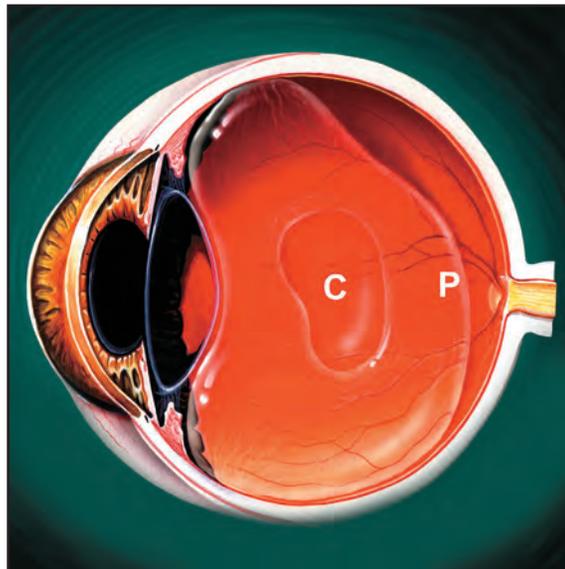


Figure 1: The vitreous in normally aging eyes. The vitreous gel in non-diabetic eyes, such as shown above, generally goes through aging changes consisting of lacunae formation (C), syneresis and posterior separation (P). It has been observed that in diabetic eyes without retinopathy, there seems to be a lower incidence of lacunae formation compared to non-diabetic eyes of a similar age group. (Art from Jaypee-Highlights Medical Publishers).



Complications from proliferative diabetic retinopathy arise as a result of the interaction between the vitreoretinal adhesions, and the vitreous contraction and can be viewed as consequences of partial posterior vitreous separation in diabetic eyes. There are mainly three complications:

- 1) vitreous hemorrhage;
- 2) tractional and/or rhegmatogenous retinal detachment; and
- 3) rapid neovascular growth.

Vitreous Hemorrhage

In the presence of a partial posterior vitreous separation, and the vitreo retinal adhesion of the vitreous cortex to the new vessels on the retinal surface, vitreous traction from eye movements on these new vessels may cause a rupture of these flimsy vessels and bleeding into the vitreous cavity may promote more vitreous condensation, more vitreous shrinkage, and more vitreous traction until the vitreo-neovascular adhesions were broken by the traction.

However, when the traction is mild and not severe enough to break the vitreo-neovascular adhesions, but just enough to cause leakage or small bleeding into the vitreous cortex or the subcortical/preretinal space, a partial posterior vitreous separation may persist. When the neovascular tissue is quickly replaced by a fibrovascular proliferation and a fibrous proliferation, the vitreoretinal adhe-

sions become more firm, and when further vitreous contraction and traction may transmit the pulling force onto the retinal surface instead of breaking the vitreo retinal adhesion, a tractional retinal detachment or retinal break may then occur.

Tractional Retinal Detachment

When the cortical vitreous is tethered to the retinal surface through strong fibrorascular or fibrotic proliferations and membranes, and when the vitreoretinal adhesions involve a wide area, and when the neighboring retina has close to normal tensile strengths, insidious vitreous contraction may result in a centripetal traction on the retina leading to a tractional retinal detachment (Figure 2).

Retinal Break and Rhegmatogenous Retinal Detachment

However, if the dense vitreo retinal adhesion involves only a small focal area, such as a pinpoint, and if the surrounding retina has compromised tissue tensile strength such as atrophic retina after extensive laser treatment, or when the surrounding retina is chronically edematous, and when the vitreous shrinkage and contraction occurs precipitously and forcefully, the centripetal tractional force onto a focal area of weakened retina may result in a retinal break. A rhegmatogenous retinal detachment may then result.

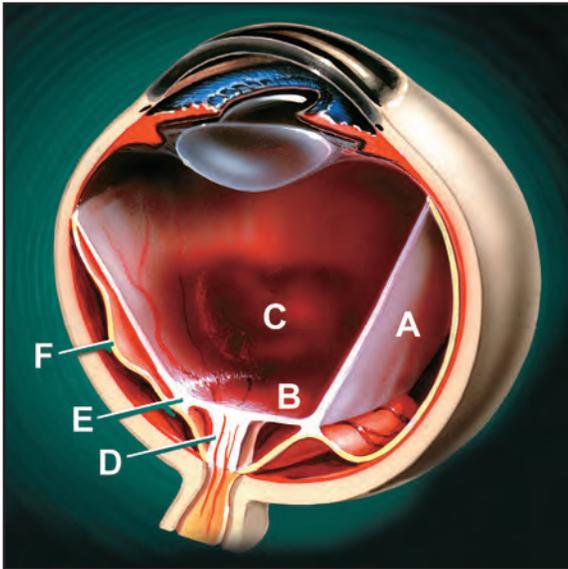


Figure 2: Traction retinal detachment from proliferative diabetic retinopathy - pathologic changes. Predominant abnormalities include anteroposterior vitreous traction caused by funnel-shaped configuration of posterior vitreous surface (A) and transverse traction from thickened posterior vitreous surface bridging over macular area (B). Hemorrhage is present in the vitreous gel (C) associated with fibrovascular proliferation from the optic nerve (D) and ring-like configuration of fibrovascular proliferation along temporal vascular arcades (E). Vitreoretinal traction has caused retinal detachment (F). (Art from Jaypee-Highlights Medical Publishers).

Retinal tears occurring under these circumstances are often difficult to detect, as they are frequently obscured by retinal or vitreous hemorrhages and at the edge of fibrovitreous membranes. Subretinal fluid and an area of mobile retina, together with signs of released vitreous traction may give clues to the presence of retinal tears.

Rapid Neovascular Growth

There are two important stimuli of retinal neovascularization. When retinal ischemia is significant enough to result in extensive areas of capillary non-perfusion, an angiogenic stimuli is postulated to be present to stimulate the proliferation of retinal new vessels. These new vessels typically occur at the area of the retina bordering the area of capillary non perfusion. There is also a second stimulus for neovascularization, namely a mechanical stimulus represented by a partial posterior vitreous separation. The separated posterior hyaloid surface provides a scaffold for new vessels to proliferate. A partial posterior vitreous separation promotes rapid neovascular growth.

I have followed a group of diabetic patients and correlated the course of their retinopathies with the status of the vitreous body on initial examination. In those eyes which had no posterior vitreous separation or had a complete posterior vitreous separation on initial examination, 95% of the eyes had stable retinopathy over an average course of 5 or more years. But in eyes which showed a partial posterior vitreous separation, 55% of the eyes had a progressive retinopathy while 38% of eyes had stable retinopathy. The difference is statistically significant.

There are other clinical observations to support the hypothesis that partial posterior vitreous separation is a powerful stimulus to rapid neovascular proliferation. New vessels are generally not detected on areas of retina



from which the vitreous has separated. Also, in eyes with proliferative diabetic retinopathy, if no posterior vitreous separation is evident, the new vessels generally progress very slowly. And in eyes in which posterior vitreous separation is complete, neovascularization tend to be quite stable and progress very little if at all. Furthermore, in eyes with early new vessels, when a complete posterior vitreous separation later takes place, new vessels can be observed to regress. Another observation includes the regression of neovascularization after vitrectomy when the posterior hyaloid membrane is excised and this regression may occur even without intraoperative or postoperative laser treatment. These are all clinical observations to support the thesis that partial posterior vitreous separation is a powerful stimulus for rapid new vessel growth.

Implications of a Partial Posterior Vitreous Separation

Based on the above clinical observations, it seems that laser treatment for diabetic retinopathy is most effective if undertaken before partial posterior vitreous separation has begun. Complete posterior vitreous separation seems to offer good prognosis in proliferative diabetic retinopathy even if new vessels are present. In eyes with proliferation changes, a partial posterior vitreous separation indicates a poor prognosis and warrants prompt and aggressive treatment. Finally, in eyes with no retinopathy or non-proliferative retinopathy, the presence of a complete posterior vitreous separation seems to protect the eyes from new vessels proliferation and progressive changes of the retinopathy. The status of

the vitreous is a good clinical parameter to follow diabetic patients with no retinopathy or early retinopathy.

A Three-Dimensional Concept

There appears to be two processes racing against time in a diabetic eye. On a two-dimensional surface, there is an angiopathy represented by neovascularization, which occurrence is dependent upon the duration and severity of the metabolic derangement. On another level, and on a three-dimensional consideration, there is a vitreopathy represented by vitreous shrinkage and posterior vitreous separation, which occur as an aging process and accelerated by diabetic changes.

Therefore, in early onset diabetes, chronic and extensive angiopathy stimulates new vessel growth before the vitreous is totally detached. Partial posterior vitreous separation results and proliferative changes and their inherent complications of vitreous hemorrhage, tractional and rhegmatogenous retinal detachment and accelerated new vessel growth frequently follow.

In late onset diabetes, posterior vitreous separation occurs before angiopathy has been significant enough to stimulate new vessel growth. Thus, non-proliferative diabetic changes generally result.

In conclusion, diabetic proliferative changes result from a race in the course of time between diabetic angiopathy and diabetic vitreopathy (posterior vitreous separation).



Diabetic Vitreoretinopathy

It is thus proposed that whereas “diabetic retinopathy” is a two-dimensional term describing the changes, mostly angiopathy, on the retinal surface, “diabetic vitreoretinopathy” or “DVR” is a three dimensional term more accurately depicting the three-dimensional dynamics between the retinal surface and the vitreous body. Therefore, proliferative diabetic retinopathy (PDR) should become proliferative diabetic vitreo retinopathy (PDVR), and non-proliferative diabetic retinopathy (NPDR) should become non-proliferative diabetic vitreo retinopathy (NPDVR). At least, these terms prompt us to think of the vitreous and examine the vitreous in diabetic eyes.

Vitreous Involvement in Diabetic Retinopathy

The vitreous has three strong attachment areas with the retina. The strongest attachment straddles the most anterior area of the retina (ora serrata) where a 4-mm circular band forms the vitreous base. Traction at the vitreous base usually is transmitted to the adjacent peripheral retina. The next strong attachment of the vitreous is at the circular zone around the optic nerve head. This zone becomes progressively weakened with increasing age, and it becomes easily separated with posterior vitreous detachment.

Bleeding from neovascular and fragile vessels in proliferative diabetic retinopathy, proliferative sickle cell retinopathy, ischemic

retinopathy secondary to retinal vein occlusion, and retinopathy of prematurity are among the most common pathological causes of vitreous hemorrhage.

The most common pathogenesis of bleeding in this group of disorders is believed to be retinal ischemia causing the release of angiogenic vasoactive factors, most notably vascular endothelial growth factor (VEGF), basic fibroblast growth factors (bFGF), and insulin-like growth factor (IGF). The second most frequent pathological mechanism for vitreous hemorrhage is tearing of the retinal vessels caused by either a break in the retina or detachment of the posterior vitreous, while the cortical vitreous is adherent to the retinal vessels. In addition, patients with sickle cell retinopathy may show a salmon-patch hemorrhage caused by blowout in the vessel wall following abrupt occlusion in the arterioles by aggregated sickled red blood cells. Other less common pathological mechanisms of vitreous hemorrhage include subretinal bleeding with secondary extension into the vitreous cavity.

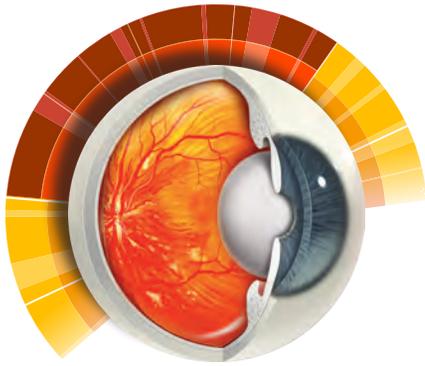
Neovascularization is observed at the borders of perfused and non-perfused retina and most commonly occur along the vascular arcades and at the optic nerve head. New vessels break through and grow along the surface of the retina and into the scaffold of the posterior hyaloid face. By themselves, these vessels rarely cause visual compromise. However, they are fragile and highly permeable. These delicate vessels are disrupted easily by vitreous traction, which leads to hemorrhage into the vitreous cavity or the preretinal space.



These new blood vessels initially are associated with a small amount of fibroglial tissue formation. However, as the density of the neovascular frond increases, so does the fibrous tissue formation. In later stages, the vessels may regress leaving only networks of avascular fibrous tissue adherent to both the retina and the posterior hyaloid face. As the vitreous contracts, it may exert tractional forces on the retina via these fibroglial connections. Traction may cause retinal edema, retinal heterotopia, and both tractional retinal detachments and retinal tear formation with subsequent detachment.

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15

Branch Retinal Vein Occlusion

LIHTEH WU, MD

Much confusion exists in the literature because central and branch retinal vein occlusions (BRVO) often are clumped and studied together. The natural history and complication rate for each entity is quite different. The treatments and their results vary from one condition to the other. Hemiretinal vein occlusions (HRVO) are probably variants of central retinal vein occlusions and, as such, will not be included in this discussion.¹ This chapter deals exclusively with BRVO.

Epidemiology

Retinal vein occlusions (branch and central) are the second most common retinal vascular diseases after diabetic retinopathy.² The Beaver Dam Study reported a prevalence of 0.6% in patients older than 43 years.³ The 15 year cumulative incidence of BRVO was 1.8% in the Beaver Dam Eye Study.⁴ A cross sectional study from 6 communities across the US

reported that the prevalence of BRVO was 0.9%. Furthermore this same study showed that the prevalence of BRVO was similar across different ethnic and racial groups.⁵ In a population-based study from Australia, the Blue Mountains Eye Study, the prevalence of BRVO in the population older than 48 years was 1.1%.⁶ The Singapore Malay Eye Study reported a 0.6% prevalence of BRVO in the Malay population of 40-80 years old living in Singapore.⁷ The Beijing Eye Study reported that the prevalence of BRVO in a Chinese population of people ≥ 40 years of age was 1.3%.⁸ No racial or gender predilection for the disease is apparent. The patients who are affected are usually in their fifth or sixth decade of life.³⁻⁷ The Eye Disease Case Control Study identified systemic hypertension as an important risk factor for BRVO. Unlike central retinal vein occlusion, diabetes mellitus and open angle glaucoma were not found to be risk factors for BRVO.⁹



Classification

Depending on the anatomic site of the arteriovenous crossing, BRVO may be classified into major BRVO and macular BRVO.¹⁰ Some authors also include HRVO as a variant of BRVO.^{10,11} However, Hayreh and Hayreh¹ have shown that a HRVO arises from an occlusion of one of the trunks in an eye with a dual trunk central retinal vein. Thus a HRVO should be considered as part of the spectrum of a central retinal vein occlusion rather than a BRVO.

Etiology

Anatomic, hypertensive, atherosclerotic, inflammatory, or thrombophilic conditions may lead to retinal endothelial vascular damage with subsequent intravascular thrombus formation. Inflammatory conditions that have been associated with a BRVO include sarcoidosis,¹² Lyme disease¹³ and serpiginous choroiditis.¹⁴ Thrombophilic conditions such as protein S deficiency,¹⁵ protein C deficiency,¹⁶ resistance to activated protein C (factor V Leiden),¹⁵ antithrombin III deficiency,¹⁵ antiphospholipid antibody syndrome,¹⁷ lupus erythematosus¹⁷ and gammopathies have also been associated with BRVO.

However, the major risk factor in the development of a BRVO appears to be anatomic. Eyes with arteriovenous crossings appear to be at risk of developing BRVO.¹⁸⁻²³ In these eyes, the thick walled artery is anterior to the thin wall vein in most cases. In the presence of systemic vascular disease the risk of oc-

clusion may be accentuated when arteriolar sclerosis results in an increased rigidity of the crossing artery which causes compression of the underlying vein. Compression of the vein diminishes the lumen by as much as a third of its baseline diameter. Turbulent flow results which in turn damages the vascular endothelium creating a local environment favorable to intravascular thrombus formation. Once the venous flow is compromised or interrupted, retinal ischemia ensues downstream from the site of occlusion. Retinal ischemia is one of the most important up-regulators of vascular endothelial growth factor (VEGF) production.²⁴ Several animal models of BRVO have shown that occlusion of a branch retinal vein leads to VEGF upregulation.^{25,26} VEGF has been shown to be a key mediator in the pathogenesis of macular edema and intraocular neovascularization.²⁷ Increased aqueous VEGF levels have been reported in human eyes with BRVO.²⁸ Furthermore the levels of VEGF correlate with the degree of macular edema and retinal ischemia.²⁹ Therefore, VEGF appears to be a promising therapeutic target in the treatment of BRVO.

Clinical Findings

The diagnosis of a BRVO is usually straightforward. Leber first described the condition ophthalmoscopically in 1877.² Most occlusions occur in the superotemporal quadrant since most arteriovenous crossings occur in this location. During the acute phase, intraretinal hemorrhages (usually flame shaped), retinal edema, and cotton-wool spots are seen in the distribution of a retinal vessel. Serous detachment of the macula may also be seen.³⁰

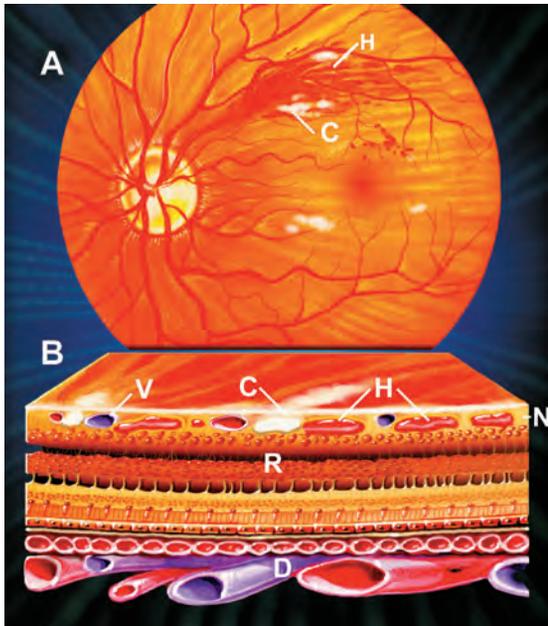


Figure 1: Branch Retinal Vein Occlusion. (A) Shows a fundus view of a branch retinal vein occlusion which produces hemorrhages (H) within the nerve fiber layer of the retina and cotton wool spots (C). (B) Shows a magnified cross section of retina (R) and choroid (D). Note the hemorrhages (H) and cotton wool spots (C) located within the nerve fiber layer (N). One can also see the retinal vein (V). (Art from Jaypee-Highlights Medical Publishers).

The horizontal raphe is respected. During the chronic stage, hemorrhages may be absent. Macular edema may be the only sign present. Telangiectatic vessels that extend across the horizontal raphe usually can be demonstrated angiographically. The upstream side of the occlusion may become fibrotic. In certain eyes with large areas of non-perfusion, retinal neovascularization may be seen. Vitreous hemorrhage with tractional retinal detachments may ensue. Further traction may create retinal breaks, creating combined rhegmatogenous and

tractional retinal detachments. Neovascular glaucoma and neovascularization at the disc are rare events with BRVO (Figure 1).

Work-Up

The Branch Vein Occlusion Study (BVOS) has recommended against extensive testing in patients with a typical BRVO.³¹ In atypical cases, i.e., young patients, bilateral cases, or patients with a personal or family history for thromboembolism, certain laboratory studies may be of use. Prothrombin time (PT), activated partial thromboplastin time (aPTT), protein C, protein S, factor V Leyden, antithrombin III, homocysteine levels, folate levels, antinuclear antibody (ANA), lupus anticoagulant, anticardiolipin, serum protein electrophoresis (SPEP) and fasting lipid levels (triglycerides included) should be ordered in these circumstances.

Angiographic Findings (Fluorescein and ICG)

In the healthy fundus, arteriovenous crossing sites are not associated with venous compression, but in the presence of arteriosclerotic or hypertensive arteriolar changes, increased compression of the vein causes a visible narrowing at the crossing site, sometimes with marked upstream dilation of the vein. Early stages of BRVO with partial venous occlusion often show this phenomenon very clearly.

In the acute stage of a partial or complete venous occlusion the fluorescein angiography shows venous engorgement upstream of the crossing, resulting in ischemia, hemorrhage



and cotton-wool spot formation. If fluorescein angiography is performed when the intraretinal hemorrhages are still present, a hypofluorescent area corresponding to the blood will block both the retinal and choroidal circulations during the early phases. In the late phases, some leakage which results from the endothelial cell damage and the increased intracapillary pressure may be seen extending beyond the hemorrhages. No other details will be seen. Therefore our recommendation is to wait until the hemorrhages have cleared before performing a fluorescein angiogram. Typical angiographic findings following clearing of the intraretinal hemorrhages include a prolonged retinal circulation time, perivenous staining in the obstructed area, evidence of capillary leakage, macular leakage consistent with cystoid macular edema, areas of capillary non-perfusion and in certain cases retinal neovascularization. With time collateral vessel remodeling and maturation may occur. These collaterals usually support enough flow to maintain some retinal function. They are best seen angiographically around the foveal avascular zone and over the temporal watershed zone. The collaterals bypass the occlusion by draining the venous blood into adjacent venous drainage areas and gradually distend, generally resulting in reduced leakage. It typically takes 6 to 24 months for the collaterals to mature and stabilize. Reduction of leakage and edema often results in an improvement in visual acuity, provided that no irreversible foveal damage has occurred.

The BVOS recommends that a fluorescein angiogram should be obtained as soon as the hemorrhages have cleared if vision is still depressed, usually 3 months after the event.³¹ The purpose is to determine the cause of visual loss (i.e., macular edema or macular ischemia) (Figures 2 and 3). If the visual loss is secondary to macular edema, laser photocoagulation in a grid pattern may be of benefit.³¹ Conversely, if macular ischemia is responsible for the loss of vision, laser photocoagulation should not be offered to the patient.³²

Over the past decade there has been a renewed interest in indocyanine green (ICG) angiography. Due to its fluorescence in the infrared, ICG penetrates blood much better than fluorescein. Even though ICG may be performed in the acute phase while the intraretinal hemorrhages are still present;³³ no one has been able to show that the information gathered from an ICG is useful in the management of a BRVO. Fluorescein angiography remains the gold standard in the management of BRVO.

Optical Coherence Tomography

Traditionally, biomicroscopic examination of the macula in combination with fluorescein angiography has been used to diagnose and manage macular edema. However it has been shown that visual function correlates better with macular thickness as compared



Figure 2: Branch Retinal Vein Occlusion. Branch retinal vein occlusion with diffuse retinal hemorrhages. (Photo courtesy of Lawrence A. Yannuzzi, M.D., selected from his extensive retinal images collection with the collaboration of Kong-Chan Tang, M.D.)



Figure 3: Fluorescein Angiogram of Branch Vein Occlusion. Venous phase of fluorescein angiogram showing superotemporal branch retinal vein occlusion. Note the retinal capillary microaneurysms (pinpoint spots of hyperfluorescence). (Photograph presented as a courtesy of William Tasman's from his classic book "Clinical Decisions in Medical Retinal Disease", Chapter 1 by Jay Federman, M.D., published by Mosby, Inc., 1994.)



to fluorescein leakage.³⁴ In addition, angiographic leakage is a qualitative test whereas retinal thickness, as measured by instruments such as the OCT, is a quantitative test. OCT has proven its value in the management and follow-up of patients with macular edema.^{35,36} Nevertheless, it should be emphasized that there is only a modest correlation between OCT measured center point thickness and visual acuity. Thus OCT is a very useful tool for the diagnosis and measurement of the response to treatment but it can't be used as a surrogate for visual acuity measurements.³⁷

Treatment

The 3 most common causes of visual loss following a BRVO are macular edema, macular non-perfusion and vitreous hemorrhage secondary to intraocular neovascularization.² Of these, macular edema is the most common. The BVOS has shown that macular grid laser photocoagulation is effective in the treatment of macular edema.³¹ If the fluorescein angiogram reveals macular non-perfusion, laser is not warranted and observation is recommended. Finkelstein reported that eyes with macular edema secondary to non-perfusion had a good visual prognosis. The median visual acuity in his series was 20/30.³² In eyes with retinal neovascularization, the BVOS has also shown that scatter photocoagulation is the treatment of choice. In eyes with other complications such as vitreous hemorrhage, tractional and rhegmatogenous retinal detachment, vitrectomy techniques should be employed.³⁸⁻⁴¹

Macular Grid Laser Photocoagulation

The current recommendation is to wait 3 months to allow for spontaneous improvement in vision and clearance of the intraretinal hemorrhages. If no improvement is seen and the hemorrhages have mostly cleared from the macular area, a fluorescein angiogram is obtained. If the fluorescein angiogram shows leakage in the macular area responsible for the decrease in vision, a macular grid laser is recommended. The laser parameters for macular grid photocoagulation used in the BVOS included a duration of 0.1 second, a spot size of 100 μm and a sufficient power to cause a medium white retinal burn. The burns were placed one spot size apart from each other in a grid fashion over the area of leakage identified in the fluorescein angiogram. The laser spots came to the edge of the capillary free zone and extended to the major arcades but not beyond them.³¹ After 3 years of follow-up care, 63% of laser treated eyes improved 2 or more lines of vision compared to 36% of control eyes.³¹ In laser treated eyes, the average improvement of visual acuity was only 1.3 lines from baseline, 40% of eyes ended up with a visual acuity $\leq 20/40$ and 12% remained with a visual acuity $\leq 20/200$.³¹ Given the modest benefits of macular photocoagulation in eyes with macular edema, new modalities have been explored in the hopes of improving these results.



Scatter Photocoagulation

Neovascularization usually occurs at the border between ischemic and non-ischemic retina. Eyes with neovascularization of the disc (NVD) are believed to have more extensive ischemia than those without NVD. According to the BVOS, approximately 40% of eyes with large areas of ischemia (>5 disc areas of non-perfusion) are at risk of developing neovascularization.⁴² Of the eyes that do develop neovascularization, 60% will have vitreous hemorrhage. The BVOS demonstrated that scatter photocoagulation reduces the prevalence of neovascularization by one half (from 40% to 20%). However, if one were to treat all eyes with non-perfusion, a large percentage of patients (60%) who would never develop neovascularization would be treated with scatter photocoagulation. If one were to treat only the eyes that develop neovascularization, the events of vitreous hemorrhage also would drop by one half (from 60% to 30%). Therefore, the recommendation is to wait until neovascularization actually develops before considering scatter photocoagulation.

Alternative Treatments for Macular Edema

Anti-VEGF

Several anti-VEGF agents are currently available in clinical practice. Both pegaptanib sodium (Macugen®, Eyetech, NY,

NY USA),⁴³⁻⁴⁵ an aptamer against VEGF165, and ranibizumab (Lucentis®, Genentech, San Francisco, CA, USA),⁴⁶⁻⁵¹ a fragment of a humanized monoclonal antibody against all VEGF isoforms, have been shown to be beneficial in the treatment of CNV secondary to age-related macular degeneration (ARMD), diabetic macular edema and central retinal vein occlusion. Bevacizumab (Avastin®, Genentech, San Francisco, CA, USA) is a humanized, recombinant monoclonal IgG antibody that binds and inhibits all VEGF isoforms. Rosenfeld et al introduced intravitreal injection of bevacizumab into clinical practice.^{52,53} Of these anti-VEGF agents, bevacizumab has been the most widely used in the treatment of BRVO.

Several retrospective and prospective case series have demonstrated that intravitreal bevacizumab at doses of 1mg up to 2.5 mg of intravitreal bevacizumab causes an improvement in visual acuity concomitant with a reduction in CMT in the short term.⁵⁴⁻⁶⁰ In a small open labeled prospective trial of short duration, Campochiaro et al 48 randomized 20 eyes with macular edema secondary to BRVO to 3 consecutive intravitreal injections of 0.3 mg or 0.5 mg of ranibizumab. At the primary endpoint of 3 months, the visual acuity improved 10 and 18 letters. By 1 week, over 80% of the excess foveal thickness was eliminated in both dose groups. In most cases multiple injections are required to maintain the benefits of therapy. The optimum dose and dosing sequence for intravitreal bevacizumab is still undetermined. It is unclear if a higher dose can provide better outcomes and/or a longer disease



free interval and reduce the burden of more frequent injections. When Rosenfeld and colleagues first injected eyes with CRVO and ARMD, they used the same dose of 1.25 mg of bevacizumab.^{52, 53} However, the intraocular levels of VEGF in different pathologies appear to differ. Funk et al⁶¹ reported a value of 121.8 pg/mL in 8 eyes with BRVO. Holecamp et al⁶² reported the vitreous levels of VEGF in 9 eyes with exudative ARMD to be 39.3 pg/mL which is much lower than the values obtained in eyes with BRVO. The Pan American Collaborative Retina Study (PACORES) Group compared the visual acuity, central macular thickness (CMT) and number of injections of 1.25 mg and 2.5 mg of intravitreal bevacizumab in eyes with macular edema secondary to BRVO with 6 months of follow-up. They found that there were no differences in any of these parameters between both doses at 6 months of follow-up.⁵⁴ One of the main weaknesses of most studies reporting on intravitreal bevacizumab for macular edema secondary to BRVO is the lack of a laser control group.⁵⁴⁻⁶⁰ This precludes a direct comparison of intravitreal bevacizumab with the gold standard of macular photocoagulation. A recent prospective comparative study of 30 eyes with 12 months duration has shown that 1.25 mg of intravitreal bevacizumab was more effective in restoring visual acuity and central macular thickness than macular photocoagulation.⁶³ All of these results suggest that in BRVO, VEGF does indeed play a major role in the pathogenesis of macular edema since blocking VEGF results in substantial improvement in macular edema.

Corticosteroids

Due to its potent anti-permeability and anti-inflammatory properties corticosteroids have been used to treat macular edema from different etiologies.⁶⁴ The problem lies in delivering therapeutic concentrations of the medication to the posterior segment of the eye. High doses of systemic corticosteroids are needed to achieve these therapeutic concentrations but at the cost of significant systemic side effects. Intravitreal delivery of corticosteroids avoids the systemic side effects from systemic therapy and at the same time permits high drug concentrations at the target tissue. Of the different corticosteroids available, intravitreal triamcinolone has been the most commonly used because of its long half life.⁶⁵⁻⁶⁸ Even though the current commercial preparation of triamcinolone has not been specifically formulated for intraocular use, animal studies have shown a lack of toxicity in the usual doses used.⁶⁹ The optimal dose has not been determined. Most retinal specialists use a dose of 4 mg in 0.1 cc however doses up to 25 mg of triamcinolone have been injected.^{67, 70} It is not clear when to inject, when to reinject or whether to use the triamcinolone as an adjunct to laser treatment or as a primary treatment. A handful of cases of macular edema secondary to BRVO treated with an intravitreal triamcinolone injection have been reported.^{70,71} The Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) Study randomized 403 eyes with BRVO to macular photocoagulation vs 4 mg of intravitreal triamcinolone



vs 1 mg of intravitreal triamcinolone. The study is fully enrolled but the results have not been published yet.^{11,37} In the hopes of reducing the possible complications from an intravitreal injection of triamcinolone, some authors have reported the use of periocular triamcinolone.^{72,73} Hayashi and colleagues compared repeated retrobulbar injections of 40 mg of triamcinolone to one intravitreal injection of 4 mg of triamcinolone and found that intravitreal triamcinolone was more effective than the retrobulbar injections at the 3 month follow-up.

Dexamethasone is a more potent corticosteroid than triamcinolone. Furthermore, intravitreal injections of dexamethasone achieves high intravitreal drug levels without any toxic effects. The main drawback of dexamethasone is its short intraocular half life of 3 hours. A biodegradable intravitreal dexamethasone implant has been designed and tested in patients with macular edema secondary to BRVO. The short term results appear quite promising.⁷⁴

Several complications arising from an intravitreal triamcinolone injection have been reported. Among them the most serious is endophthalmitis. Sterile technique is essential to avoid this uncommon but dreaded complication. A sterile endophthalmitis, presumably secondary to the preservatives, has also been reported.^{75,76} An increase in intraocular pressure and cataractogenesis are known side effects of steroids in general.^{77,78} Further study is warranted to define what role if any, intravitreal corticosteroids will have in the management of macular edema secondary to BRVO.

Laser-Induced Chorioretinal Anastomosis

Bypass of the normal retinal venous drainage channels is attempted by creating a communication between the obstructed vessel and the choroid by literally blasting a hole through the RPE and choriocapillaris with a high energy Argon or YAG laser.⁷⁹ Problems with this technique are the lack of reliability in creating an anastomosis (most series report a 30-50% success rate) and its complications.⁸⁰ Complications from the procedure include tractional retinal detachment and vitreous hemorrhage.

Vitreectomy

Vitreectomy has been shown to increase the oxygenation in the vitreous cavity.⁸¹⁻⁸³ In a cat model of BRVO, the pre-retinal oxygen tension was significantly decreased in non-vitreotomized eyes as compared to vitreotomized eyes.⁸⁴ Several series have documented the benefits of vitreectomy for eyes with macular edema secondary to BRVO.^{85, 86} Several theories exist as to how a vitreectomy improves macular edema. These include an increased oxygenation of the vitreous cavity, removal of cytokines such as VEGF from the vitreous cavity and the release of vitreomacular traction.

Since virtually all BRVO's occur at arteriovenous crossings and arterial compression is thought to be the major cause of this condition, Osterloh and Charles⁸⁷ recommended



lifting the artery from the underlying vein to relieve the compression. In this technique a regular 3 port pars plana vitrectomy is performed. The intraocular pressure is raised to prevent bleeding. The site of the obstruction is identified with the help of a pre-operative fluorescein angiogram. Then with a bent MVR blade or a special knife, the sheath is opened and the artery lifted from the vein. Several uncontrolled small series have reported good results with regards to improving macular edema and macular perfusion.⁸⁷⁻⁸⁹ On the other hand, others have reported a lack of efficacy of this procedure. In fact the benefits ascribed to sheathotomy may be explained by the vitrectomy itself.⁹⁰⁻⁹² Some surgeons have also recommended peeling of the internal limiting membrane.^{93,94} However, Arai et al⁹⁵ in a comparative trial found no additional benefit from peeling the internal limiting membrane in eyes with macular edema secondary to BRVO.

Final Remarks

BRVO is a common retinal vascular condition. Perfused macular edema is responsible for most cases of visual dysfunction following a BRVO. Despite all the promising results from experimental therapies such as vitrectomy, anti-VEGF agents and corticosteroids; macular photocoagulation remains the treatment of choice. Before any of these alternative treatments can be adopted as the standard of care, they must be proven to be more efficacious than macular photocoagulation.

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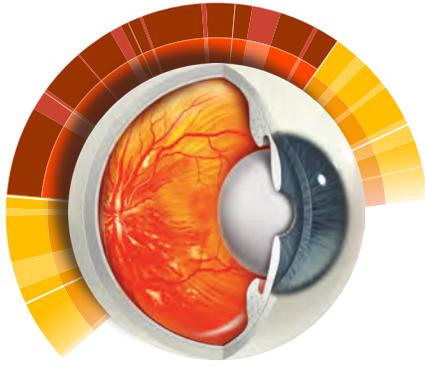
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16

Central Retinal Vein Occlusion

LIHTEH WU, MD

The exact pathogenesis of the thrombotic occlusion of the central retinal vein is not known. Various local and systemic factors play a role in the pathological closure of the central retinal vein.¹

The central retinal artery and vein share a common adventitial sheath as they exit the optic nerve head and pass through a narrow opening in the lamina cribrosa. Because of this narrow entry in the lamina cribrosa, the vessels are in a tight compartment with limited space for displacement. This anatomical position predisposes to thrombus formation in the central retinal vein by various factors, including slowing of the blood stream, changes in the vessel wall, and changes in the blood. Up until the third month of intrauterine life, the fetal central retinal vein consists of a dual trunk that surrounds the central retinal artery. Right before birth, one of the trunks disappears. However in up to 20% of eyes, the dual trunk persists. If one of the trunks becomes occluded a hemi retinal vein occlusion will result.¹ This chapter deals exclusively with CRVO.

Epidemiology

Retinal vein occlusions (branch and central) are the second most common retinal vascular diseases after diabetic retinopathy.² The Beaver Dam Study reported a prevalence of 0.1% in patients older than 43 years.³ The 15 year cumulative incidence of CRVO was 0.5% in the Beaver Dam Eye Study.⁴ A cross sectional study from 6 communities across the US reported that the prevalence of CRVO was 0.2%. Furthermore this same study showed that the prevalence of CRVO was similar across different ethnic and racial groups.⁵ In a population-based study from Australia, the Blue Mountains Eye Study, the 10 year cumulative incidence of CRVO in the population older than 48 years was 0.4%.⁶ The Singapore Malay Eye Study reported a 0.2% prevalence of CRVO in the Malay population of 40-80 years old living in Singapore.⁷ The Beijing Eye Study reported that the prevalence of CRVO in a Chinese population of people ≥ 40 years of age was 0.1%.⁸ No racial or gender predilection for the disease is apparent.



Epidemiologic studies have identified cardiovascular disease, diabetes mellitus, age over 55 years, hypertension and glaucoma as important associations with CRVO.⁹ Despite these associations, most authorities believe that medical treatment of the associated systemic conditions bear little influence in the outcome of the ocular complications.

Pathogenesis

The exact pathogenesis of a CRVO is currently unknown. A key component in the pathogenesis of a CRVO is narrowing of the central retinal vein. The central retinal artery and vein share a common adventitial sheath at the level of the lamina cribrosa.^{10,11} Here the vessel walls touch one another. Long standing systemic hypertension and arteriosclerosis cause enlargement and hardening of the central retinal artery which compresses the adjacent central retinal vein narrowing its lumen. Other conditions such as papilledema, optic disc drusen and inflammation may also cause narrowing of the central retinal vein. When the lumen of the central retinal vein becomes narrow enough, turbulent flow ensues creating the proper conditions for thrombus formation.¹² Histopathologic studies have shown that CRVO occurs secondary to thrombus formation at the level of the lamina cribrosa or posterior to it.^{12,13} Once a thrombus forms, blood becomes stagnant causing the capillary and venous pressure to rise. At the same time the retina becomes hypoxic from the stagnant blood leading to damage of the capillary endothelial cells and extravasation of blood and its constituents into the extracellular space. There is increasing evidence that VEGF

plays a key role in the pathogenesis of macular edema and intraocular neovascularization secondary to CRVO. Experimental models have shown that hypoxia triggers VEGF up-regulation.¹⁴⁻¹⁶ In enucleated human eyes with CRVO and neovascular glaucoma, *in situ* hybridization techniques localized the VEGF producing retinal cells to the ischemic regions of the retina.¹⁷ In eyes with ischemic CRVO, there was correlation between increasing VEGF aqueous levels, retinal neovascularization and vascular permeability.¹⁸ Intravitreal injections of VEGF into a non-human primate eye produces a retinopathy that mimics the clinical picture of a CRVO.¹⁹ VEGF inhibition in non-human primate eyes reverses iris neovascularization in a CRVO model.²⁰ Increased aqueous VEGF levels have been reported in human eyes with CRVO.²¹ Furthermore the levels of VEGF correlate with the degree of macular edema and retinal ischemia.²² Therefore, VEGF appears to be a promising therapeutic target in the treatment of CRVO.

Classification

Over the years it has been recognized that CRVO encompasses a wide spectrum of disease. Thus many terms such as impending, incipient, partial, incomplete, venous stasis retinopathy, hemorrhagic, perfused, non-perfused, indeterminate, ischemic and non-ischemic have appeared in the literature.²³⁻²⁶ In essence there is a recognition that some CRVO are mild and have a relatively good prognosis whereas other CRVO are severe and have catastrophic visual consequences. Currently the most accepted terms are non-ischemic or non-perfused vs ischemic or perfused.²⁶

It must be emphasized that the differentiation between an ischemic vs non-ischemic CRVO can't be made with just a biomicroscopic examination of the fundus.²⁷ Of all the funduscopic features of a CRVO, the degree of intraretinal hemorrhages is the only finding with a small correlation with ischemia. Other features such as optic nerve edema, cotton wool spots, venous dilation and macular edema have no correlation whatsoever. The presence of an afferent pupillary defect, a visual acuity of $\leq 20/200$, reduced b-wave and decreased b/a amplitude in the electroretinogram, peripheral constriction on perimetry and capillary occlusion > 10 disc diameters on fluorescein angiography all correlate with ischemic CRVO. Thus to accurately classify an eye with CRVO as ischemic or nonischemic all the above information is necessary.^{27,28}

Clinical Findings

Most patients complain of a sudden loss of vision. Some patients may complain of transient obscurations of vision that last from a few seconds to minutes followed by complete recovery to normal. Patients with neovascular glaucoma complain of ocular pain and redness.

Acutely, CRVOs are characterized by some degree of dilation and tortuosity of the retinal veins. Intraretinal hemorrhages are seen in all four quadrants (Figure 1). The severity of these hemorrhages vary from a few scattered superficial hemorrhages to extensive full retinal thickness hemorrhages with break through into the vitreous cavity. Patches of cotton wool spots may be seen. The optic nerve is usually swollen. In the chronic stages, the hemorrhages may have disappeared. Optic nerve head collaterals and macular edema may be the only residual

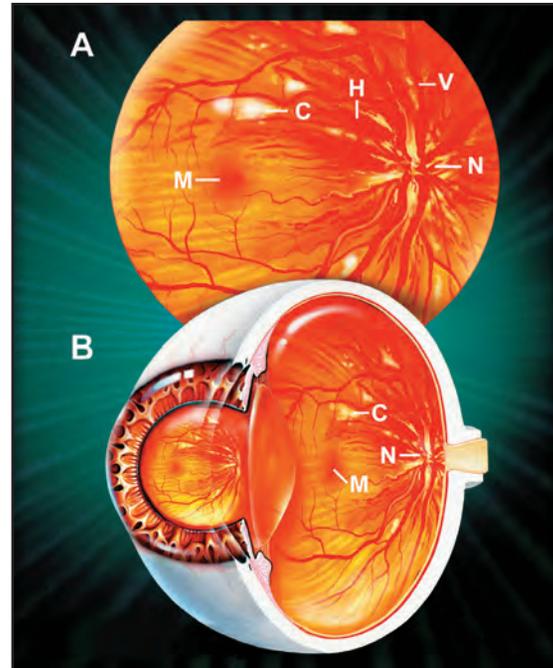


Figure 1: Central Retinal Vein Occlusion. (A) The fundus view shows the main features of central retinal vein occlusion. They include: optic disc swelling (N), dilation of the retinal veins (V), retinal hemorrhages (H), macular edema (M), and cotton wool spots (C). (B) Shows the ophthalmoscopic view through the pupil and its corresponding cross section. (Art from Jaypee-Highlights Medical Publishers).

ophthalmoscopic evidence that a prior CRVO had occurred. The major complications resulting from CRVO are macular edema resulting from diffuse capillary leakage and neovascular glaucoma as a result of the secretion of angiogenic factors such as vascular endothelial growth factor (VEGF) from areas of non-perfused retina. The development of neovascular glaucoma usually occurs within the first 3 months following development of a CRVO (90 day glaucoma).



Angiographic Findings

The angiographic findings depend on great part on the ophthalmoscopic findings at the time of the fluorescein angiogram. In all eyes there is a delay in the filling of the retinal circulation. Blockage of the underlying retinal circulation and choroidal circulation may occur if extensive intraretinal hemorrhages are present. Invariably there is some degree of capillary non-perfusion. This may range from minimal to extensive and serves as the basis of the classification of CRVO into perfused or non-perfused types. There is also some leakage from the optic nerve head secondary to disc edema. The walls of the retinal vessels are damaged from the disease process and become stained with fluorescein in the late stages.

Optical Coherence Tomography

Traditionally, biomicroscopic examination of the macula in combination with fluorescein angiography has been used to diagnose and manage macular edema. However, it has been shown that visual function correlates better with macular thickness as compared to fluorescein leakage.²⁹ In addition, angiographic leakage is a qualitative test whereas retinal thickness, as measured by instruments such as the OCT, is a quantitative test. OCT has proven its value in the management and follow-up of patients with macular edema.^{30,31} Nevertheless, it should be emphasized that there is only a modest correlation between OCT measured center point thickness and visual acuity. Thus OCT is a very useful tool for the diagnosis and measurement of the response to treatment but it can't be used as a surrogate for visual acuity measurements.³²

Treatment

The Central Vein Occlusion Study (CVOS)

The CVOS was a multicenter, randomized controlled clinical trial that studied the visual outcomes following grid laser photocoagulation in eyes with macular edema, following panretinal photocoagulation in eyes with non-perfused CRVO, and the natural history of eyes with perfused CRVO.^{26,33-35} In the CVOS, eyes were arbitrarily classified as non-perfused if the fluorescein angiogram revealed more than 10 disc areas of capillary non-perfusion. This differentiation is important because up to one third of non-perfused eyes in the CVOS developed anterior segment neovascularization. In some eyes, fluorescein angiography was unable to determine perfusion status because the hemorrhages blocked the underlying capillaries. Once the hemorrhages cleared allowing a good quality fluorescein angiogram to be performed, it became apparent that these eyes behaved like non-perfused eyes. It is noteworthy that 15% of eyes initially classified as perfused became non-perfused after 4 months of follow-up. An additional 19% progressed to non-perfusion after 3 years of follow-up. Risk factors for disease progression included a baseline visual acuity of 20/200 or worse, recent onset and extensive intraretinal hemorrhages. Presenting visual acuity is an important prognostic factor. Two thirds of eyes with an initial visual acuity of 20/40 or better retained that level of vision whereas 74% of eyes with an initial visual acuity of 20/250 or worse maintained that degree of visual loss (Figures 2 and 3).

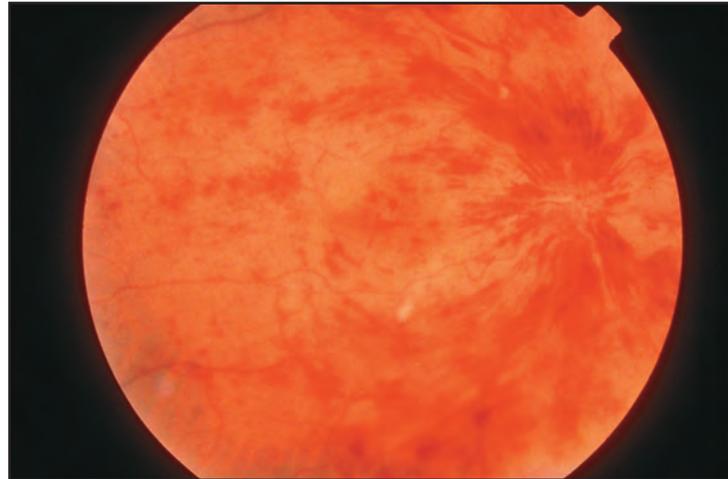


Figure 2: Central Retinal Vein Occlusion. Central retinal vein occlusion with extensive intraretinal hemorrhages. (Photo courtesy of Lawrence A. Yannuzzi, M.D., selected from his extensive retinal images collection with the collaboration of Kong-Chan Tang, M.D.)

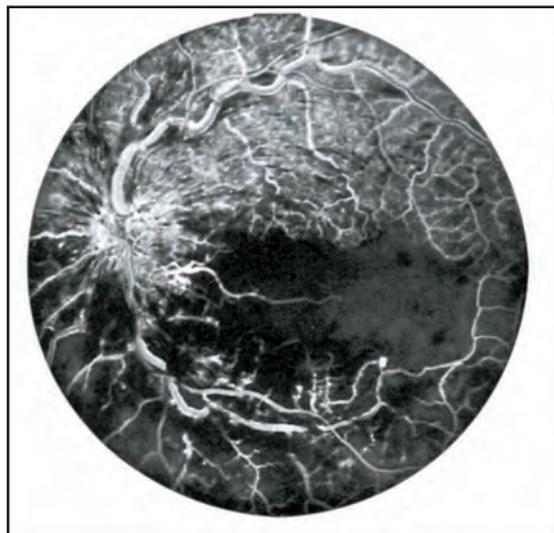


Figure 3: Fluorescein Angiogram in Central Retinal Vein Occlusion. Fluorescein angiogram of another patient showing extensive capillary non-perfusion consistent with an ischemic central retinal vein obstruction. (Photograph presented as a courtesy of William Tasman's from his classic book "Clinical Decisions in Medical Retinal Disease", Chapter 1 by Jay Federman, M.D., published by Mosby, Inc., 1994.)



The CVOS demonstrated that grid laser treatment of macular edema was of no visual benefit despite the elimination of the macular edema in those eyes that were treated. It also showed that the best strategy in non-perfused eyes was to delay panretinal photocoagulation until 2 clock hours of iris neovascularization or any angle neovascularization was observed. In order to achieve this, the CVOS has recommended a monthly visit for the first 8 months where undilated slit lamp examination of the pupillary border and gonioscopy are performed to detect early neovascularization. Panretinal photocoagulation is effective in controlling anterior segment neovascularization. About 8.5% of eyes that developed anterior segment neovascularization progressed to neovascular glaucoma that was refractory to medical treatment despite panretinal photocoagulation. None of these eyes required enucleation.

Alternative Treatments

Anti-VEGF

Several anti-VEGF agents are currently available in clinical practice. Both pegaptanib sodium (Macugen®, Eyetech, New York, NY USA),³⁶⁻³⁸ an aptamer against VEGF165, and ranibizumab (Lucentis®, Genentech, San Francisco, CA, USA),³⁹⁻⁴⁴ a fragment of a humanized monoclonal antibody against all VEGF isoforms, have been shown to be beneficial in the treatment of CNV secondary to age-related macular degeneration (ARMD), diabetic macular edema and central retinal vein occlusion. Bevacizumab (Avastin®, Genentech, San Francisco, CA, USA)

is a humanized, recombinant monoclonal IgG antibody that binds and inhibits all VEGF isoforms. Rosenfeld et al introduced intravitreal injection of bevacizumab into clinical practice.^{45,46} Of these anti-VEGF agents, bevacizumab has been the most widely used in the treatment of CRVO.

Several uncontrolled retrospective and prospective case series have demonstrated that intravitreal bevacizumab at doses of 1mg up to 2.5 mg causes an improvement in visual acuity concomitant with a reduction in CMT in the short term.⁴⁷⁻⁵⁷ However in other studies, the visual acuity did not improve despite the improvement in CMT.⁵⁸⁻⁶¹ Similar results have been obtained in 3 small uncontrolled prospective case series studying ranibizumab for CRVO.^{40,41,44} A multicenter, randomized, double masked Phase 2 trial showed that pegaptanib sodium was also beneficial in the short term.³⁸ Experience has shown that multiple injections are required in these eyes. All of these results suggest that in CRVO, VEGF does indeed play a major role in the pathogenesis of macular edema since blocking VEGF results in substantial improvement in macular edema.

Isovolemic Hemodilution

Some patients with CRVO exhibit abnormal red cell deformability, increased plasma viscosity, increased hematocrit and an increased fibrinogen level. By reducing hematocrit levels, plasma viscosity is lowered which may lead to improved retinal microcirculation and perfusion. Several randomized clinical trials have documented an improvement in visual acuity, arteriovenous



passage time and clinical appearance.⁶²⁻⁶⁴ The procedure appears to be well tolerated. Despite the improvements in visual acuity these studies suffer from several limitations. The numbers were usually small and multiple interventions such as xenon photocoagulation, pentoxifylline, prednisolone that were not controlled for were used.⁶²⁻⁶⁴

Corticosteroids

Due to its potent anti-permeability and anti-inflammatory properties corticosteroids have been used to treat macular edema from different etiologies.⁶⁵ The problem lies in delivering therapeutic concentrations of the medication to the posterior segment of the eye. High doses of systemic corticosteroids are needed to achieve these therapeutic concentrations but at the cost of significant systemic side effects. Intravitreal delivery of corticosteroids avoids the systemic side effects from systemic therapy and at the same time permits high drug concentrations at the target tissue. Of the different corticosteroids available, intravitreal triamcinolone has been the most commonly used because of its long half life.⁶⁶⁻⁶⁹ Even though the current commercial preparation of triamcinolone has not been specifically formulated for intraocular use, animal studies have shown a lack of toxicity in the usual doses used.⁷⁰ The optimal dose has not been determined. Most retinal specialists use a dose of 4 mg in 0.1 cc however doses up to 25 mg of triamcinolone have been injected.^{68,71} It is not clear when to inject, when to reinject or whether to use the triamcinolone as an adjunct to laser treatment or as a primary treatment. Several studies have reported improved visual outcomes and a reduction in central macular thickness following intravitreal triamcino-

lone.⁷²⁻⁷⁴ The Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) Study randomized 262 eyes with CRVO to macular photocoagulation vs 4 mg of intravitreal triamcinolone vs 1 mg of intravitreal triamcinolone. The study is fully enrolled but the results have not been published yet.^{32,75}

Dexamethasone is a more potent corticosteroid than triamcinolone. Furthermore, intravitreal injections of dexamethasone achieves high intravitreal drug levels without any toxic effects. The main drawback of dexamethasone is its short intraocular half life of 3 hours. A biodegradable intravitreal dexamethasone implant has been designed and tested in patients with macular edema secondary to CRVO. The short term results appear quite promising.⁷⁶ A long acting intravitreal fluocinolone acetonide sustained drug delivery implant has recently been approved by the FDA for the use in macular edema secondary to chronic uveitis.⁷⁷ Fourteen eyes with macular edema secondary to CRVO were implanted with the fluocinolone implant and followed for 1 year.⁷⁸ There was an improvement in visual acuity and central macular thickness but at a relatively high price. Cataract developed in all the 5 phakic eyes and 13 out of 14 eyes required a medical or surgical intervention to decrease intraocular pressure.⁷⁸

Several complications arising from an intravitreal triamcinolone injection have been reported. Among them the most serious is endophthalmitis. Sterile technique is essential to avoid this uncommon but dreaded complication. A sterile endophthalmitis, presumably secondary to the preservatives, has also been reported.^{79,80} An increase in intraocular pressure and cataractogenesis are known side effects of steroids in general.^{81,82}



A recent review concluded that there was inadequate evidence for the use of intravitreal steroids for macular edema secondary to CRVO due to a lack of randomized clinical trials and well designed observational studies.⁸³ Further study is warranted to define what role if any, intravitreal corticosteroids will have in the management of macular edema secondary to CRVO.

Chorioretinal Anastomosis

In an attempt to restore venous outflow, McAllister and Constable^{84, 85} have pioneered the creation of a chorioretinal anastomosis in order to bypass the occlusion in eyes with perfused CRVO. To successfully create a chorioretinal anastomosis, Bruch's membrane and the retinal vein must be ruptured with the laser. They recommend rupturing Bruch's membrane first with a 50 μm spot size, 0.1 sec duration and argon power levels of 2.5 to 3 W. Once Bruch's is ruptured, a second spot is placed at the edge of the retinal vein. Successful rupture of the vein is seen in about a third of cases treated with the argon laser. In those cases where the vein hasn't ruptured, 3.5 to 5 mJ of YAG laser power is used to rupture the vein. Using the above technique, a chorioretinal anastomosis can be created in 67% of cases. Complications arising from this treatment include distal vein closure, fibrovascular proliferation and vitreous hemorrhage.^{84,85} They caution against using this technique in non-perfused eyes. Rapid fibrovascular proliferation that requires immediate panretinal photocoagulation may be seen in those eyes. Others have attempted to create a chorioretinal anastomoses via a surgical approach using a variety of different surgical techniques with varying results.⁸⁶⁻⁸⁸ A small random-

ized study compared 6 laser treated eyes with 5 control eyes. All laser treated eyes had a patent chorioretinal anastomosis documented on fluorescein angiography. Although there was no statistically significant change in vision in the laser treated eyes, a trend towards better vision and decreased central macular thickness were observed in the laser treated eyes.⁸⁹

Thrombolytic Therapy

Forty patients diagnosed with a CRVO of less than a week duration were randomized to an intravenous streptokinase infusion of 100 000 units/hr in 100 mL of saline for 72 hours vs observation. After a year of follow-up, there were only 5 eyes that were treated with streptokinase that suffered a decrease in vision as compared to 12 eyes in the control group. However, 3 eyes in the streptokinase group developed a massive vitreous hemorrhage and remained blind. It must be beared in mind though, that this study was reported in 1974 when vitrectomy techniques were just being developed.⁹⁰ Systemic thrombolytic therapy with tissue plasminogen activator (t-PA) was found to be effective in a pilot study. However, the complications from such treatment included a fatal stroke and 3 patients developed severe intraocular bleeding.⁹¹ In view of these complications, local intravitreal t-PA delivery has been tested in a few uncontrolled case series.⁹²⁻⁹⁴ Cannulation of the retinal venous system with injection of t-PA following a standard vitrectomy has been successfully accomplished.^{95,96} Nevertheless the significance of the results remains unclear since the procedures have not been compared to controls or even standard vitrectomy.



Vitrectomy

Vitrectomy has been shown to increase the oxygenation in the vitreous cavity.⁹⁷⁻⁹⁹ In a cat model of BRVO, the pre-retinal oxygen tension was significantly decreased in non-vitrectomized eyes as compared to vitrectomized eyes.¹⁰⁰ Several series have documented the benefits of vitrectomy for eyes with macular edema secondary to BRVO.^{101,102} Several theories exist as to how a vitrectomy improves macular edema. These include an increased oxygenation of the vitreous cavity, removal of cytokines such as VEGF from the vitreous cavity and the release of vitreomacular traction.

The posterior hyaloid may exert tangential traction that contributes to the pathogenesis of macular edema in CRVO.¹⁰³⁻¹⁰⁵ In eyes with non-ischemic CRVO with macular edema, the prevalence of macular edema was reduced from 76% in eyes with the posterior hyaloid attached to 25% in eyes with a posterior vitreous detachment.¹⁰³ A number of retrospective case series have reported improved visual acuity and a reduction in central macular thickness following vitrectomy.¹⁰⁵⁻¹⁰⁷

Opremcak¹⁰⁸ postulated that a CRVO is the result of a compartment syndrome where the scleral outlet forms the bottleneck. He proposed that relieving pressure on the occluded vein via a radial optic neurotomy would improve venous outflow. In this technique, following a standard vitrectomy a single radial incision is made into the scleral ring and adjacent sclera on the nasal part of the optic disc. Radial optic neurotomy remains controversial and several case series have reported numerous complications.¹⁰⁹

In summary several different surgical techniques based on vitrectomy including radial optic neurotomy, internal limiting membrane peeling and posterior hyaloid peeling have been advocated for the treatment of CRVO.^{101,108,110} Unfortunately, most of these studies are uncontrolled, have small numbers and the use of multiple interventions does not allow for direct comparisons between studies.

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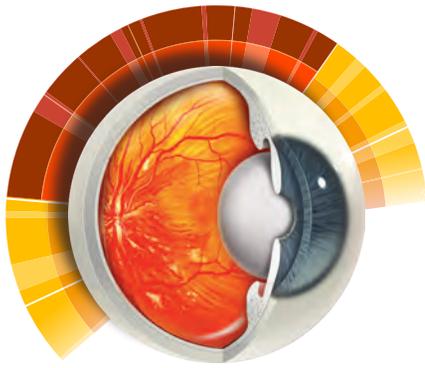
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17

Management of Active Retinopathy of Prematurity

CARLOS A. ABDALA, MD.,
ANA T. PERALTA, MD.

Retinopathy of prematurity (ROP) is a vitreoretinal proliferative disease in premature infants that may cause severe or complete visual impairment, and it is a major cause of reversible blindness worldwide. The two largest multicenter cohort studies report similar incidence of the disease, CRY-ROP Study of 65.8%, and ETROP Study of 68% among infants <1251 g, reassuring it remains a common important problem in the neonatal intensive care unit.¹

The fundamental process underlying the development of ROP is incomplete vascularization of the retina and the ophthalmoscopic findings derive from this abnormal development. ROP is characterized by the proliferation of fibrovascular tissue at the border of vascular and avascular retina, giving rise to the various stages of ROP² (Figure 1).

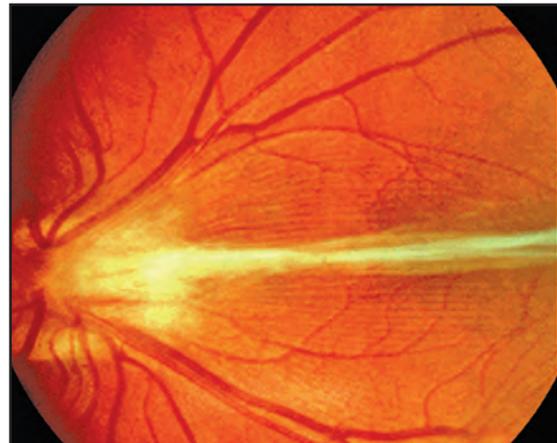


Figure 1: This picture shows a dense white membrane emerging from the optic disc with a retina fold on the macula area as a sequelae of an ROP stage IV b.



Multicenter trials have defined the manner in which ROP is screened, monitored and treated.

The Multicentre Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Study for the first time established the beneficial effect of cryotherapy of peripheral avascular retina on eyes with threshold ROP. *Threshold ROP* is defined as 5 contiguous or 8 cumulative clock hours of stage 3 ROP in zone I or II, in the presence of plus disease (dilated and tortuous posterior pole vessels). This has demonstrated to significantly reduce by half the progression to an unfavorable outcome such as macular dragging, retinal detachment or retrolental cicatrized formation. Of the 9751 infants enrolled at 23 centers in the USA of birth weight less than 1251g, 291 that progressed to threshold disease participated and were randomly assigned to have either cryotherapy in one eye or no cryotherapy in the fellow eye.³

Cryotherapy was shown to significantly reduce both functional and structural primary outcomes of threshold ROP in treated versus control eyes throughout the follow-up (Figure 2). Unfavorable structural outcome, defined as posterior retinal detachment, retinal fold involving the macula or retrolental tissue, was proven to be reduced to 45.8% at 12 months. Consistent with CRYO-ROP previous reports, the beneficial effects of structural outcome persisted long-term, and at 15 year follow-up 30% of treated eyes had unfavorable outcome versus 51% of control eyes.⁴



Figure 2: Extensive Cryoablation in Peripheral Retina.

Visual function for near and distance acuity was assessed monocularly, and the attempted procedure showed that treated eyes had significantly better visual acuity than control. For the 5 1/2 year outcome visual acuity showed a reduction in unfavorable outcomes of 47.1% in treated versus 61.7% in control eyes.⁵ Unfavorable visual acuity outcomes at 15 years was found in 44.7% of treated versus 64.3% of control eyes.

Treatment at threshold in the CRYO-ROP resulted in approximately a 50% reduction in the rate of retinal detachment. CRYO-ROP showed that 44.4% of eyes with history of severe ROP had a visual acuity at 10 years of age of 20/200 or worse, and of those only

45.5% had visual acuity 20/40 or better. With the hope of improving the rate of unfavorable outcome, the indications for treatment were questioned and the need to identify earlier treatment criteria for the eyes at highest risk for developing threshold ROP and/or unfavorable visual or structural outcome in the absence of treatment was discussed.

Data of 828 infants with birth weight less than 1251g in 26 participating center in the USA were collected for the Early Treatment for Retinopathy of Prematurity (ETROP) study from 2000 to 2002, designed to detect if some eyes with ROP of less than threshold could benefit from retinal ablation therapy. In the study infants were randomized to early peripheral retinal ablation or standard treatment (follow-up until regression or treatment at threshold disease) if they developed *prethreshold* ROP, which was defined as any ROP in zone I that was less than threshold, or in zone II stage 2 with plus disease and stage 3 without plus disease, or zone II stage 3 with plus disease but fewer than threshold. A risk analysis program based on natural history data from CRYO-ROP study (RM-ROP2) was used; if the risk progression to unfavorable outcome in absence of treatment was <15%, the eye was termed "high-risk pre-threshold", and randomization occurred. Eyes with >15% risk according to RM-ROP2 were termed "low-risk pre-threshold" and followed.⁶

Functional outcome was measured monocularly with as used in CRYO-ROP, and showed a reduction in unfavorable outcomes with earlier treatment, from 19.8% to 14.3%. Structural examinations were performed at 6 and 9 months, with unfavorable results reduced from 15.6% in conventionally treated to 9.0% in high-risk pre-threshold treated eyes, at 9 months, with outcomes stable at the 2 year follow-up.

The results of this study showed it was possible to identify characteristics of ROP that predict high-risk eyes for retinal detachment and blindness (Figure 3), therefore most likely to benefit from early peripheral retinal ablation, while minimizing treatment of pre-threshold eyes likely to show spontaneous regression of

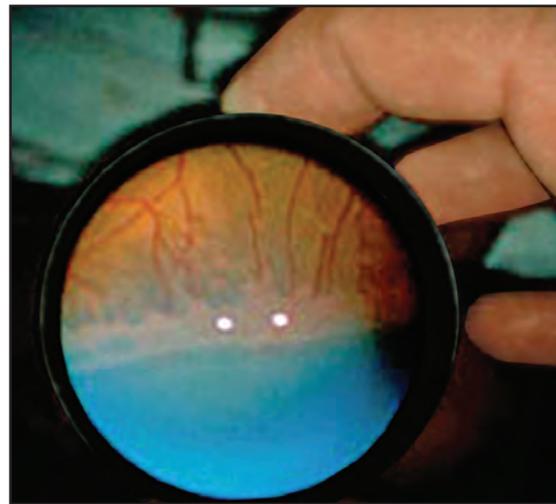


Figure 3: Retinal blood vessels fail to reach the retinal periphery and multiply abnormally where they end.



ROP. Ocular complications rates were similar in both groups, whereas systemic complications were higher following treatment at high-risk pre-threshold, attributed to receiving retinal ablative therapy at an earlier postmenstrual age.

Therefore, with the ETROP it was established the beneficial effect of treatment at high-risk pre-threshold ROP on structural outcome and visual acuity outcome provides further support for retinal ablative therapy for eyes with:

- *Type I* ROP defined as: zone I, any stage with plus disease; zone I, stage 3 ROP without plus disease; or zone II, stages 2 or 3 with plus disease.

The analysis supported a “wait and watch” with continued serial examinations, as opposed to peripheral retinal ablation, (unless eyes progress to type I ROP or threshold), for eyes with:

- *Type II* ROP defined as: zone I, stage 1 and 2 without plus disease, or zone II, stage 3 without plus disease.⁷

Screening

Babies born at or before 32 weeks gestational age, or weighing 1500g or less, or weighing between 1500 and 2000g requiring supplemental oxygen, or with unstable course and who are thought to be at high risk, should be screened for ROP by an ophthalmologist with expertise in this matter. Clinical studies suggest screening should begin 4-6 weeks post-natal age or within the 31st or 33rd week of postconceptional or postmenstrual age (whichever is later) to detect the onset of threshold disease. Indirect ophthalmoscopy with a 28 or 20 D lens under wide pupil dilation is the gold standard for screening. Subsequent review should be at 1-2-weekly intervals, depending on severity, until retinal vascularization reaches zone 3 or until 45 weeks of postmenstrual age.

Screening with digital imaging with wide angle retinal fundus camera (RetCam) is now used as an alternative method, as shown in the photographic screening for ROP study (photo-ROP) where remote interpretation of digital fundus images is a useful adjunct to conventional bedside ROP screening by indirect ophthalmoscopy, with an excellent diagnostic sensitivity when image quality is high.⁸



Indications for Therapy in Active ROP

The CRYO-ROP study first established ablation therapy for:
THRESHOLD:
<ul style="list-style-type: none"> • Stage 3 disease involving 5 contiguous or 8 cumulative clock hours in zone I or II in the presence of plus disease (dilation and tortuosity of the posterior retinal blood vessels)
After findings for ETROP trial, recommendations for treatment as follows:
PRE-THRESHOLD Type I: <i>Retinal ablation therapy for:</i>
<ul style="list-style-type: none"> • Zone I, any stage ROP with plus disease • Zone I, stage 3 ROP, with or without plus disease • Zone II, stage 2 or 3 ROP, with plus disease
PRE-THRESHOLD Type II: <i>Continued serial examinations for:</i>
<ul style="list-style-type: none"> • Zone I, stage 1 or 2 ROP, with no plus disease or • Zone II, stage 3 ROP with no plus disease
√ Plus disease: at least two quadrants of dilation and tortuosity of posterior retinal vessels

Laser Treatment

In spite of new advances in the understanding of the treatment of ROP, the basic tools available have not changed dramatically. Since 1980's retinal ablation therapy anterior to the fibrovascular ridge has been proven to be successful method of treating active ROP.

Cryotherapy was first used as an effective treatment for preventing progression of ROP. However, cryotherapy may be associated with significant systemic and ocular complications, such as postoperative lid edema hemorrhage, laceration and chemosis of conjunctiva, myopia and preretinal and vitreous hemorrhage. The need for conjunctival dissection, the technical difficulty of placement of the cryo-probe for



posterior zone 2 or 1 and the nitrogen tank not readily portable, has made most ophthalmologists to use laser therapy rather than retinal cryoablation.⁹ When used, cryotherapy is applied in contiguous single spots to the avascular retina in 360 degrees anterior to the ridge until whitening of the retina is observed. Today, indications for cryopexy instead of laser in ROP include poor fundus visibility, lack of availability of laser and lack of expertise in laser of the treating ophthalmologist.

The CRYO-ROP trial showed that ablation of peripheral avascular retina with cryotherapy was of benefit in threshold ROP. Laser photocoagulation of avascular retina has replaced cryotherapy as the established treatment for ROP in most centers for various reasons. Although no randomized trial has been conducted on the scale of the CRYO-ROP study, smaller studies have shown laser treatment to be at least as effective as cryotherapy in treatment of active ROP. NagE, Connelly et al published a 10-year follow-up randomized trial comparing laser photocoagulation with cryotherapy for threshold ROP. Outcomes showed that compared with cryotherapy, eyes treated with laser photocoagulation were 5.2 times more likely to have a 20/50 or better BCVA, and eyes treated with cryotherapy were 7.2 time more likely to develop retinal dragging compared to laser treatment. This 10-year follow-up is the largest of its kind and shows the superiority of laser, in better structural and functional outcome, over cryotherapy.¹⁰

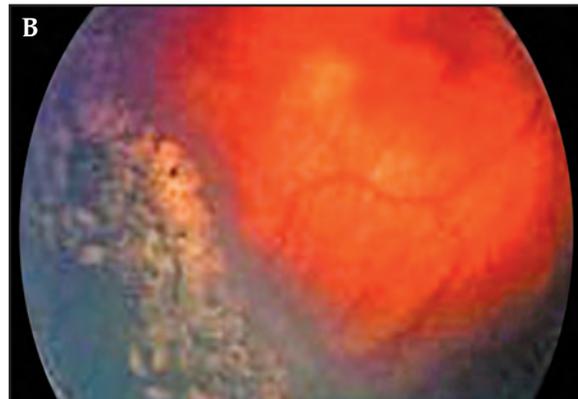
Laser photocoagulation with confluent or near confluent application of burns using indirect ophthalmoscopy has gained wide acceptance and is the gold standard for ablation of the avascular retina in ROP. Indirect

ophthalmoscopic laser is considered to be technically easier, induces less inflammation and stress on the neonate, and to be at least equivalent to cryotherapy in terms of outcome.¹¹

Laser treatment is applied to the avascular retina immediately anterior to the ridge of extraretinal fibrovascular proliferation and extending to the ora serrata for 360 degrees in all cases (Figure 4 A-B). A moderately intense gray-white burn is the desired target intensity, and often ranges from a power of 150mW to 400mW and duration of 0.2 to 0.3 seconds. Focus on retina is essential to decrease the risk of laser absorption by other tissues rather than retina. The number and density of laser burns required for a complete treatment has remained controversial and can have a profound effect on ability to halt progression. Many reports have described burn spacing placed 0.5-1 burn width apart (near confluent), with some describing patterns of less than or equal to one-half burn widths (scatter laser pattern). Less dense laser treatment or "skip areas" may lead to higher rates of treatment failure and need for retreatment. As comfort increased with these techniques, a trend towards more dense treatment has been observed. Recent reports have suggested a more complete destruction of the avascular retina with continuous laser photoablation show improved results. Banach et al compared the outcome in two consecutive groups of patients treated with two different laser photocoagulation patterns, dense versus less dense. The rate of progression in the near confluent laser treatment group was only 3.6% overall compared to 29% in the less dense pattern¹², concluding a dense pattern may reduce the rate of progression and the rate of re-treatment of the disease.¹³



Figure 4 A-B: **A)** Indirect Argon laser treatment in retinopathy of prematurity. **B)** Laser Application spots in Peripheral Area of Retina. The goal of this treatment is to destroy the retina that is deprived of retinal vessels. This helps to shrink the new vessels and prevents the formation of dense scars that usually follow.



Recent studies show the average number of spots applied has increased by 265% to 2163 applications per eye, which reflects the changing philosophy towards increased laser burn density in the avascular retina as the accepted burn pattern approaches near confluence.¹⁴

Tennant and Macnamara report the mean number of burns range from approximately 950 for zone II and over 2000 for zone I disease¹⁵, and vary considerably depending on the posterior extent of the ridge, but more than the number of burns is the adequate coverage. There is no direct correlation between covered area and number of laser burns

applied as the size of the laser burn varies depending on the distance of the aspheric lens from the eye, dioptric power of lens, burn intensity and duration.

It can be performed under general anesthesia with intubation or under intravenous sedation or with local anesthesia, depending on surgeon's preference and infant's medical condition. Treatment is carried out using an indirect laser system with a 28 D or 20 D



hand held aspheric lens, under wide pupil dilation using sclera depression after topical anesthesia applied to the eye and placement of a lid speculum. The most common complication is "skip areas" leading to continued abnormal vascularity with progression to retinal detachment. Retreatment may be necessary in eyes with persistent plus disease, active stage 3 disease and localized tractional detachment, in which a scleral buckling procedure can be performed in the latter. When retreatment is necessary, it is applied confluent to previously untreated areas which show continued activity, and applying laser in vascular retina over the fibrovascular ridge is useful.¹⁶ Despite timely and thorough laser some infants will have poor anatomic and visual prognosis due to retinal detachment.

Other complications of laser therapy are rare and include inadvertent macular burns, anterior segment ischemia, cataract, burns in cornea, iris or tunica vasculosa lentis, vitreous an choroidal hemorrhage. Diode red (810nm) is preferable to argon green (514nm) in treating ROP because of reduced risk of cataract. Long-term adverse effects include peripheral visual field loss and possibly an increased risk of late-onset retinal detachment because of tears at the edge of treatment scars in the presence of abnormal vitreous traction. Laser therapy may increase the tendency toward myopia, however, multiple studies report a relationship between ROP and myopia.

Immediately after laser treatment, steroid drops, mydriatics and topical antibiotic may be applied. Follow-up examinations should be scheduled every 1-2 weeks until regression

of plus disease and fibrovascular proliferation occurs.

Additional Therapy

It has been established that ROP is directly related to the release of angiogenic factors such as vascular endothelial growth factor (VEGF), which is also a trigger for neovascularization in proliferative retinopathies. With the use of intravitreal injections of anti-VEGF drugs as medical treatment for ocular diseases caused by neovascularization, the use of antiangiogenics for treatment of ROP opens the minds of new investigations were this therapy can be considered as an optional treatment when gold standard is not effective.

Although some authors have reported treatment of ROP with antiangiogenics as a primary therapy. Mintz-Hittner et al reported a case series of 22 eyes that never received laser, treated successfully with one intravitreal injection of bevacizumab in stage 3 ROP, concluding the use of bevacizumab (with no laser therapy) was safe and effective in this small case series.¹⁷ Likewise, Quiroz-Mercado et al reported the use of intravitreal injection of bevacizumab in 18 eyes in different stages of ROP who had either no response to conventional laser therapy or difficult to treat because of poor visualization or at high-risk pre-threshold or threshold, and found neovascular regression in 17, concluding the use of bevacizumab may be promising in the treatment of patients with ROP¹⁸, but further studies need to be performed to determine safety and long-term results.



Some other authors have presented the use of antiangiogenic in ROP when laser treatment failed. Rychwalski and Abdala et al report 2 case series, one of 10 eyes with ROP, which in spite of thorough laser photocoagulation, had progression and were treated with antiangiogenic as a rescue therapy (closure of retinal panphotocoagulation in ridge combined with intravitreal bevacizumab). All 10 eyes treated with rescue therapy stopped evolution of the disease.¹⁹ A second case series by the same authors, Abdala and Rychwalski, in 14 eyes with severe types of ROP (threshold disease with severe plus disease, or stage 4a or 4b) received rescue therapy as primary treatment, finding involution in over half of eyes treated within four weeks, and the other half after an additional injection of bevacizumab and laser on the ridge for residual disease, concluding this combination therapy might be useful in halting ROP progression for severe cases and delivers promising results.²⁰

Currently, a multicenter trial of intravitreal bevacizumab in ROP that does not respond to laser therapy is being conducted in the United States.

It is important to consider other mediators are also involved in the pathogenesis of ROP, such as insulin-like growth factor 1 (IGF-1). It is a non-oxygen-regulated factor, which is normally supplied by placenta and amniotic fluid in an increased manner through gestation, and drops at low levels after birth in preterm infants. Chen and Smith found that low serum levels of IGF-1 in premature babies directly correlate with the severity of clinical ROP and associated with lack of vascular growth and subsequent proliferation. The authors suggest that restoration of IGF-1 to

normal levels found in utero might prevent the disease by allowing normal vascular development. Clinical trials are actually being planned to restore IGF-1 to levels in utero in premature babies to evaluate if this supplement can prevent or reduce the severity.²¹

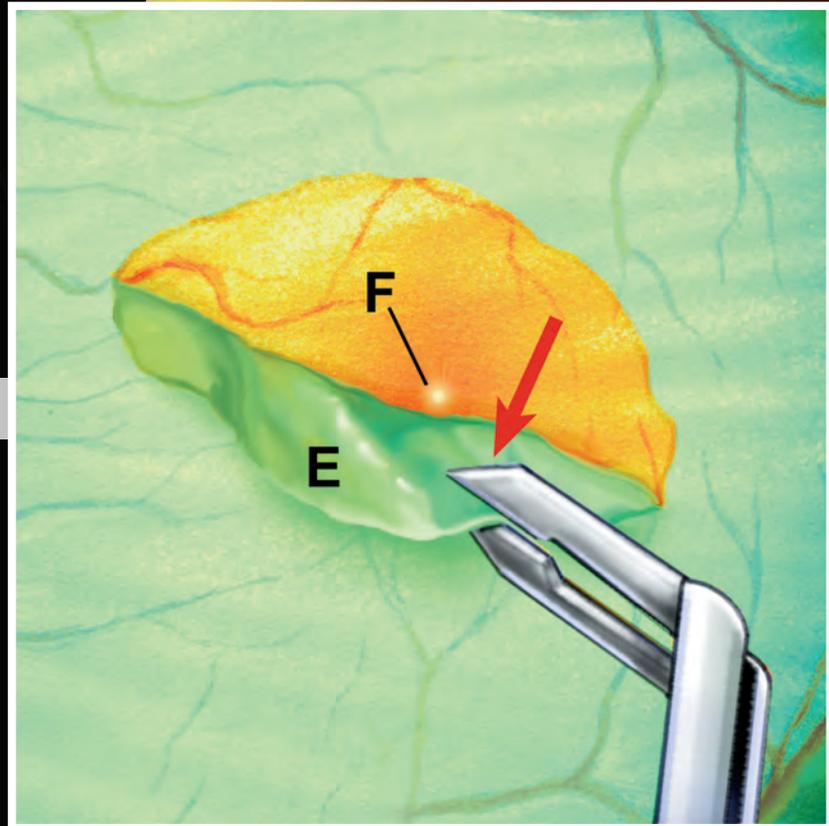
The discovery of the important role of VEGF and IGF-1 in the development of ROP is a step forward in understanding the pathophysiology and opens minds for future therapeutic medical treatment.

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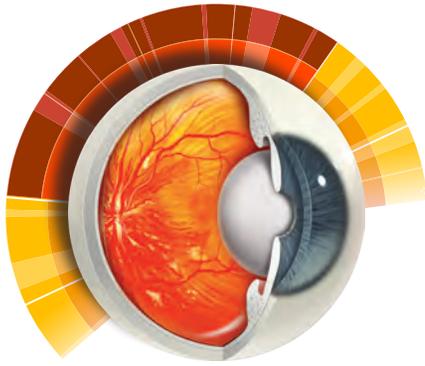
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Section 5 Macular Diseases



18

Evaluation of Age-Related Macular Degeneration

KETAN LAUD, MD.,
JASON S. SLAKTER, MD.

The Present Realities of ARMD

Age-related macular degeneration (AMD) is the leading cause of permanent central visual loss in the United States in patients 60 years of age and older affecting 8 million people throughout the United States.^{1,2} Throughout the world, particularly in economically developing countries, cataract remains the leading cause of legal blindness. The visual morbidity induced by cataract can be reversed with cataract extraction and intraocular lens implantation. In contrast, age-related macular degeneration leads to irreversible visual impairment with progressive diminution of central vision and frequent visits to a retinal specialist, resulting in a significant utilization of health care resources. AMD will become more prevalent in the future as a result of longer life expectancy and the increasing number of elderly people worldwide, particularly the non-exuda-

tive (dry) type, (Figures 1, 2, 4 and 5) which constitutes the majority of cases and which leads to a progressive diminution of central vision. The disease leads to an extensive decline in quality of life and increased need of daily living assistance resulting in a loss of independence in the later years of life of those affected.

Definition and Classification

Age-related macular degeneration can be defined as a progressive, degenerative disease of the retinal pigment epithelium (RPE), Bruch's membrane and choriocapillaris (Figure 1C, 2C, 3C) typically affecting individuals 50 years of age and older.³

Clinical diagnosis of AMD is usually made in the presence of soft or exudative drusen (Figures 4 and 8), focal hyperpigmentation of the RPE, RPE and neurosensory

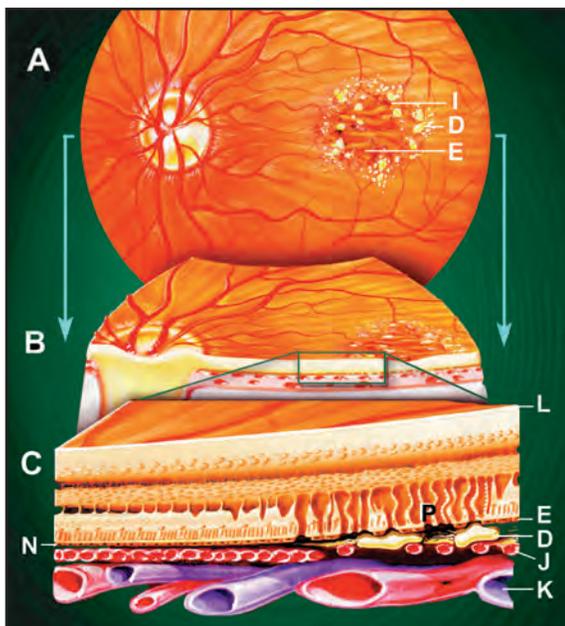


Figure 1: Anatomy and Pathology of Non-Exudative, Geographic ("Dry") Macular Degeneration. Fundus view (A) shows an example of non-exudative, geographic atrophic "dry" macular degeneration where atrophy of the retinal pigment epithelium predominates. Notice the clinical signs of drusen (D) which can appear as discrete subretinal bodies, confluent masses or hard glinting lesions, usually yellowish in color. Darker intraretinal pigment (I) may or may not be present. Retinal pigment epithelium atrophy (E) is identified by prominence of the underlying choroidal vessels. From the oblique cross section (B), an area is magnified in (C) to show the direct relationship between clinical ophthalmoscopic fundus view above and its corresponding cellular pathology. Pathology includes subretinal drusen (D) and atrophy of the RPE (E). Compare the disorganized RPE cell layer at (E) on the right to the more normal configuration at (N) on the left. Most importantly, though not clinically visible, there is definite loss of photoreceptors (P) in the area of degeneration (compare with normal photoreceptor layer on the left). Other anatomy: inner limiting membrane (L), choriocapillaris (J) and large choroidal vessels (K). (Art from Jaypee - Highlights Medical Publishers).

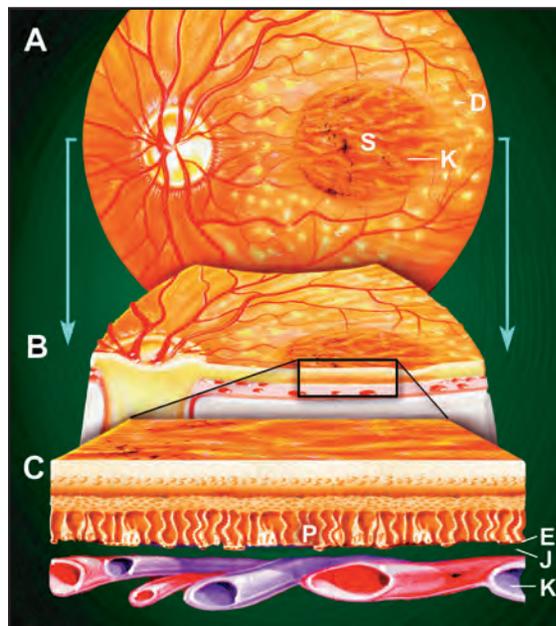


Figure 2: Anatomy and Pathology of Non-Exudative, Geographic ("Dry") Macular Degeneration with Extensive Choroidal Sclerosis. Fundus view (A) shows an example of non-exudative, geographic "dry" macular degeneration with extensive choroidal sclerosis (S). There is a clear demarcation between normal retina and the extensive atrophy of the retinal pigment epithelium, photoreceptors and choriocapillaris of the macular area. The large choroidal vessels (K) can be seen through these degenerated layers. Note surrounding drusen (D). From the oblique cross section (B), an area is magnified in (C) to show the direct relationship between clinical ophthalmoscopic fundus view above and its corresponding cellular pathology. Pathology includes atrophy of the RPE (E - note that there are only a few RPE cells in this layer), loss of photoreceptors (P) and atrophy of the choriocapillaris (J - note that choriocapillaris is virtually non-existent in this area). The large choroidal vessels (K) which become visible in the fundus view are noted beneath the degenerated layers. (Art from Jaypee - Highlights Medical Publishers).

detachments, RPE atrophy, choroidal neovascularization (Figures 3C, 6C, 7C and 9), geographic atrophy (Figure 5) or disciform scarring of the macula (Figure 11). The latter, however, is the unfortunate, irreversible end result of choroidal neovascularization

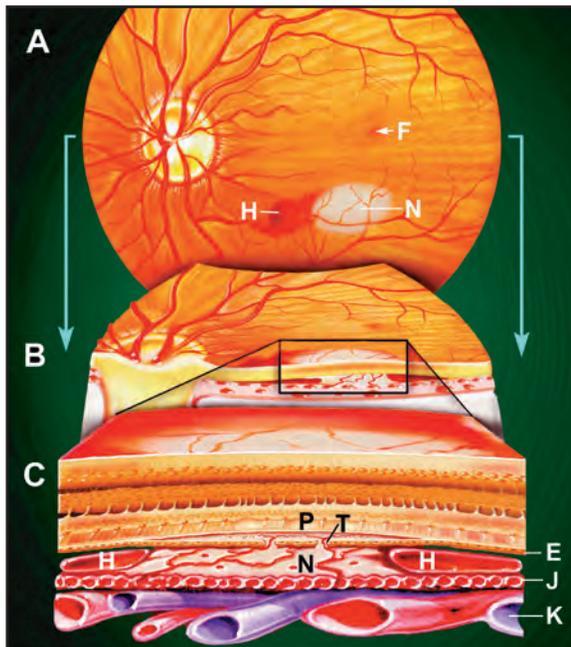


Figure 3: Anatomy and Pathology of Exudative, (“Wet”) Macular Degeneration with Extrafoveal Neovascularization. Fundus view (A) shows an example of exudative “wet” macular degeneration with an extrafoveal neovascular membrane (N) and limited subretinal hemorrhage (H) just at the margin of the paramacular retinal vessels surrounding the fovea (F). From the oblique cross section (B), an area is magnified in (C) to show the direct relationship between clinical ophthalmoscopic fundus view above and its corresponding cellular pathology. Pathology reveals that the retina is slightly elevated over a neovascular membrane (N). Note vessels emanating from the choriocapillaris (J), into the neovascular membrane (N) and into the sub-RPE and subretinal spaces, passing through small breaks (T) in the retinal pigment epithelial cell layer (E). There is some atrophy of photoreceptors in this area (P). Subretinal blood (H) is seen to either side of the neovascular membrane. Large choroidal vessels (K). (Art from Jaypee - Highlights Medical Publishers).

AMD can be broadly classified into the non-exudative (dry) and the exudative (wet, neovascular) subtypes. The non-exudative, or dry form of AMD accounts for a vast majority of patients with AMD but is responsible for a significant minority of cases with severe central visual loss (20/200 or worse). The rates of visual loss however, are different between the 2 subtypes. Changes in visual symptoms are dependent on the variety and severity of an individual eye’s involvement. Non-exudative manifestations of AMD such as drusen and RPE alterations are frequently asymptomatic (Figure 4). Larger drusen may lead to mild focal distortion or atrophy, producing central and paracentral scotomas (Figure 8) along with a gradual diminution of central acuity.

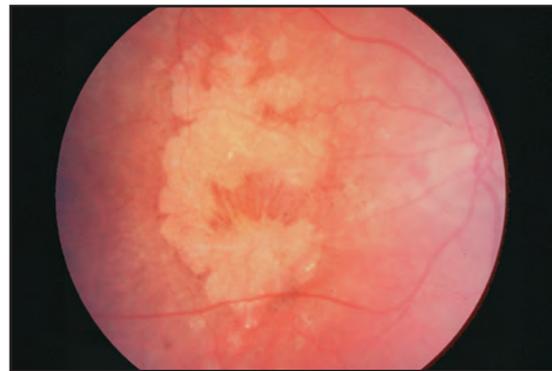


Figure 4: ARMD - Geographic, Dry, Non-Exudative Type. Geographic atrophy associated with drusen. Early stages of the disease. (Photo courtesy of Lawrence A. Yannuzzi, M.D., selected from his extensive retinal images collection with the collaboration of Kong-Chan Tang, M.D.)

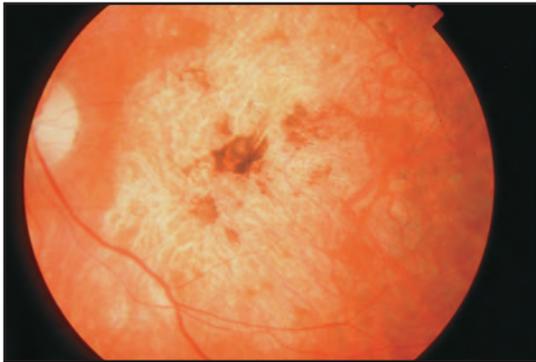


Figure 5: Geographic, Dry, Non-Exudative Type. Geographic atrophy with hyperpigmentation, metaplasia and scarred macula. Later stages of the disease. (Photo courtesy of Lawrence A. Yannuzzi, M.D., selected from his extensive retinal images collection with the collaboration of Kong-Chan Tang, M.D.)

In contrast, there is rather sudden onset of visual loss in the exudative subtype with central scotomas, and metamorphopsia. Metamorphopsia may give the perception that images are smaller (i.e., micropsia) or larger (macropsia) than they really are. The changes often appear as alterations in straight lines or surfaces, which appear wavy in the involved eye.

The hallmark of the disease in both subtypes is the presence of drusen, metabolic waste products of the retinal pigment epithelium (RPE) which deposit between the RPE and the underlying Bruch's membrane. Other ophthalmoscopic findings commonly observed in the non-exudative AMD are pigmentary changes, both in the form of hypo and hyperpigmentation of the RPE, degenerative changes of the RPE and geographic atrophy.

In the so-called "wet" or "exudative" form of the disease, new abnormal vessels in the form of fine capillary networks develop

from the choriocapillaris and invade the macula either in the sub-RPE space (type 1 choroidal neovascularization) or through the RPE in the sub-retinal space (type 2 choroidal neovascularization).⁴ There is escape of fluid from these vessels leading to accumulation of subretinal fluid, hemorrhage and secondary detachment of the RPE, Bruch's membrane and surrounding macular tissues. Exudation from these new abnormal vessels distorts the normal foveal architecture and can lead to permanent visual loss (Figures 3, 6, 7, 9, 10, 11, 12). Although a minority of patients with age-related macular degeneration manifest the exudative form of the disease, the majority of patients with severe central visual loss (20/200 or worse) from AMD have the exudative form. Clinical manifestations include serous or hemorrhagic detachment of the retinal pigment epithelium or neurosensory retina, presence of subretinal or sub-retinal pigment epithelial hemorrhages, intraretinal edema, lipid deposition, RPE hyperplasia and subretinal fibrosis. The end result of these successive changes is disciform scarring of the macula (Figure 11). Distinguishing exudative AMD from non-exudative AMD is critical as novel therapeutic strategies with intravitreal anti-VEGF therapy have been shown to significantly improve vision in conditions complicated by CNV, especially when performed early in the course of the disease.

Risk Factors

Although AMD is a multifactorial syndrome with multiple causative factors a variety of risk factors have been well delineated. Age is clearly a significant risk factor for AMD with more than 15 percent of Caucasian women 80 years and older having advanced AMD.⁵

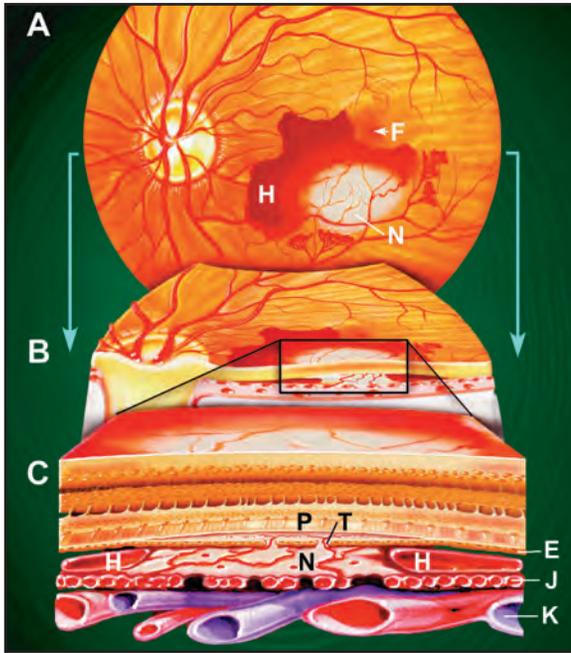


Figure 6: Anatomy and Pathology of Exudative (“Wet”) Macular Degeneration with Juxtafoveal Neovascularization. Fundus view (A) shows an example of exudative “wet” macular degeneration with a juxtafoveal neovascular membrane (N) and subretinal hemorrhage (H) extending into the foveal vascular zone but not quite to the center (F). From the oblique cross section (B), an area is magnified in (C) to show the direct relationship between clinical ophthalmoscopic fundus view above and its corresponding cellular pathology. Pathology reveals that the retina is slightly elevated over a neovascular membrane (N). Note vessels emanating from the choriocapillaris (J), into the neovascular membrane (N) and into the sub-RPE and subretinal spaces, passing through small breaks (T) in the retinal pigment epithelial cell layer (E). There is some atrophy of photoreceptors in this area (P). Subretinal blood (H) is seen to either side of the neovascular membrane. Large choroidal vessels (K). (Art from Jaypee-Highlights Medical Publishers)

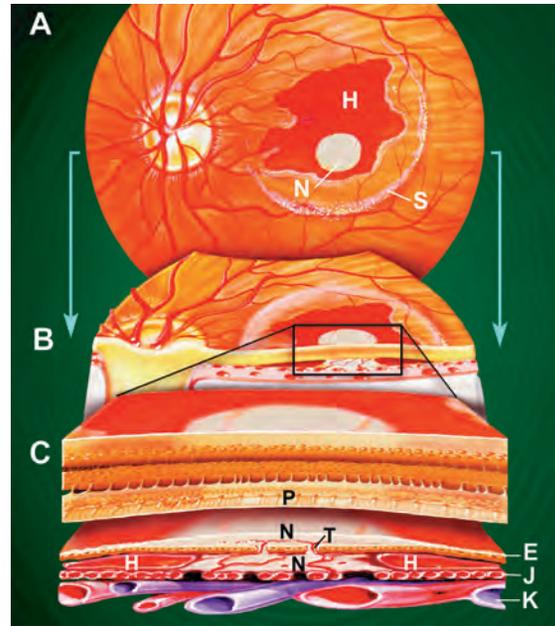


Figure 7: Anatomy and Pathology of Exudative (“Wet”) Macular Degeneration with Direct Subfoveal Neovascularization. Fundus view (A) shows an example of exudative “wet” macular degeneration with direct subfoveal neovascular membrane (N) and subretinal hemorrhage (H). Note the serous retinal detachment (S). From the oblique cross section (B), an area is magnified in (C) to show the direct relationship between clinical ophthalmoscopic fundus view above and its corresponding cellular pathology. Pathology reveals that the retina is moderately elevated (serous detachment) over the neovascular membrane (N). Note vessels emanating from the choriocapillaris (J), into the neovascular membrane (N) and into the sub-RPE and subretinal spaces, passing through small breaks (T) in the retinal pigment epithelial cell layer (E). There is some atrophy of photoreceptors (P) in this area. Subretinal blood (H) is seen to either side of the neovascular membrane. Large choroidal vessels (K). (Art from Jaypee-Highlights Medical Publishers.)



Other associated risk factors include drusen characteristics, visible light, diet, cigarette smoking⁶, cardiovascular risk factors and genetic predisposition. One study conducted by the Age Related Eye Disease Study group was to describe the association of demographic, behavioral, medical, and non-retinal ocular factors with the incidence of neovascular age-related macular degeneration (AMD) and central geographic atrophy. In this clinic-based prospective cohort study individuals with early or intermediate AMD were included at baseline. After controlling for age, gender, and AREDS treatment group, smoking and BMI were found to be modifiable factors associated with progression to advanced AMD.⁷ A significant modifiable risk factor was dietary intake of lipid. It was determined that a higher intake of omega-3 long-chain polyunsaturated fatty acid intake was inversely associated with exudative AMD.⁸ Another case control study determined that patients with exudative AMD were more likely to have hypertension⁹ and it is prudent to have optimal hypertensive control with AMD patients.

Genetic Factors

Both genetic and environmental factors are implicated in the risk of developing AMD. Studies demonstrating familial aggregation^{10,11}, twin studies¹²⁻¹⁶, segregation and linkage analysis¹⁷, genome-wide scans^{18,19}, and candidate gene studies²⁰ have affirmed the heritability of AMD. One familial aggregation study from the population-based Rotterdam Study found first-degree relatives of patients with late AMD developed AMD at an increased rate at a relatively young age.¹⁰ In another familial aggregation study, age-related

maculopathy was significantly higher among first-degree relatives of case probands (23.7%) compared with first-degree relatives of control probands (11.6%).¹¹ In addition relatives of 78 case probands with exudative disease had a significantly higher prevalence of maculopathy (26.9%) compared with relatives of the 72 unaffected control probands (11.6%).¹¹ One twin study compared concordance of age-related macular degeneration in monozygotic and dizygotic twin pairs. The concordance rate of AMD was 100% (25 of 25) in monozygotic and 42% (five of 12) in dizygotic twin pairs.¹³ In a US based study of 840 twin pairs, 331 had no signs of maculopathy, 241 had early signs, while 162 had intermediate AMD and 106 had advanced AMD.¹²

In early 2005, three research groups independently reported evidence of a strong association of the Tyr402His polymorphism in the complement H factor (CFH) gene and the development of AMD.²¹⁻²³ In individuals homozygous for the risk allele, the likelihood of AMD is increased by a factor of 7.4.²³ The implication of CFH was described by Hageman and Andersen who reported the presence of complement factors within the basement membrane and drusen that are typically seen in AMD eyes.^{24,25} Since the identification of CFH, LOC387715/ARMS2/HTRA1, C2, C3, CFB have been identified as AMD susceptibility genes.²⁶⁻²⁹ Single nucleotide polymorphisms in these genes are associated with an increased risk for progression of AMD and subsequent visual loss. Future studies will attempt to elucidate how the polymorphism affects CFH function, identify the other genes involved in AMD, and the development of promising genetic therapy which are currently in human trials.



Retinal Pigment Epithelium (RPE)

The retinal pigment epithelium (RPE) is fundamental to normal retinal function. Within its central position between the photoreceptor layer of cells (rods and cones) and the choriocapillaris (Figures 1C and 2C), it has a variety of essential functions which are metabolic, biochemical and physical. These include maintenance of the blood-retina barrier, transport of metabolites and other factors important for cell function from the choroid to the retina and vice versa. It is also essential in the processing of rhodopsin as part of the visual cycle and maintenance of retinal adhesion.³⁰⁻³²

The RPE is one of the highly specialized body tissues that rely on self-renewal and not regeneration. Its slow, continued, progressive failure in its many functions leads to significant changes in the surrounding macular tissues, ultimately causing retinal degeneration. Compare the normal photoreceptor cell layer, RPE, Bruch's membrane, choriocapillaris and other surrounding macular tissues of normal retina with the abnormal changes shown in Figures 1C through Figure 3 and Figures 6-7.

The gradual failure of the RPE is a result of the increasing difficulty in processing cellular waste over time. The photoreceptor outer segments are being constantly shed and phagocytosed by the RPE. A byproduct of photoreceptor turnover is the accumulation of undigested residual bodies within the RPE

in the form of lipofuscin.³³ This process of photoreceptor turnover requires degradation of the shed rods and cones and the elimination of this cellular waste through Bruch's membrane which is adjacent to the RPE. Some of this cellular debris does not degrade and becomes accumulated within the RPE cells, slowly increasing with age, particularly in the macula in the form of drusen.

The metabolism of the RPE largely depends on the maintenance of the integrity of Bruch's membrane (see Figures 1C through 3, 6-7). Bruch's membrane is a five layer structure consisting of outer basement membranes of the RPE and choriocapillaris, and two collagenous zones surrounding a single elastic zone.³⁴ It is situated between the RPE and the choriocapillaris and serves as a filter for the passage of nutrients and waste products between the two structures. Changes in Bruch's membrane begin in the macula as early as the teen years. There is a progressive secondary thickening of Bruch's membrane by a wide range of substances, including various forms of collagen, granular debris, and mineralized deposits. This thickening of Bruch's membrane is also made worse by the progressive accumulation of lipids as a function of age. The severity of these changes increases dramatically beyond the sixth decade of life.³⁵⁻³⁷ These alterations in Bruch's membrane continuously contribute to problems with the integrity of the RPE cell layer, thereby interfering with the normal transport of water, essential metabolites, and various modifiers of cellular activity within the macula, eventually leading to its dysfunction in a variety of forms (as illustrated in this Chapter).

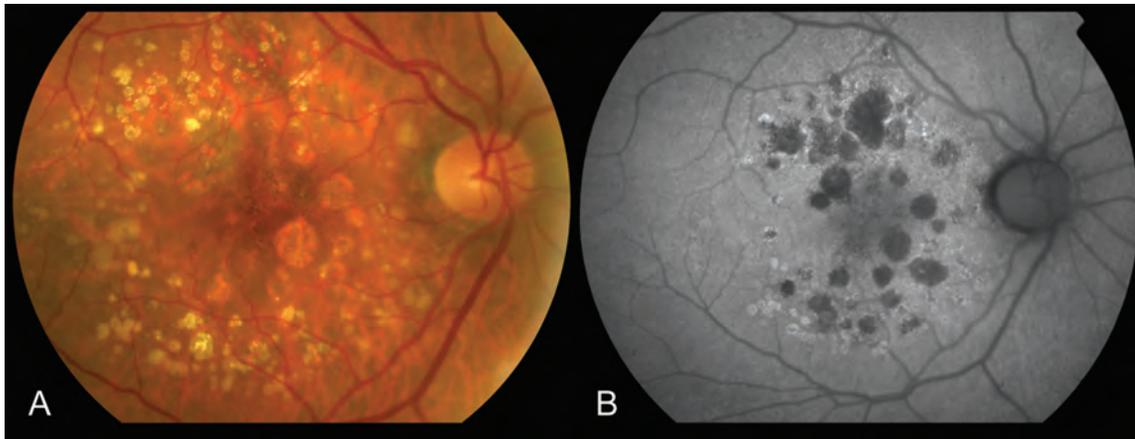


Figure 8. Non-exudative AMD. A) Color photograph of the right eye demonstrating a multitude of non-exudative manifestations of AMD including scattered hard and soft drusen and retinal pigment epithelial (RPE) atrophy. B) Fundus autofluorescence of the same eye better delineates area of RPE atrophy, characterized by multiple, circular areas of hypo-autofluorescence.

Figure 9: Exudative ARMD. Exudative maculopathy caused by choroidal subretinal neovascularization. Subretinal fluid, hemorrhage and lipid develop as a consequence of the neovascularization. (Photo courtesy of Lawrence A. Yannuzzi, M.D., selected from his extensive retinal images collection with the collaboration of Kong-Chan Tang, M.D.)



Clinical significance of Drusen

Morphologically, drusen can be classified into hard and soft varieties, which can be differentiated clinically. Hard drusen are small discrete nodules that appear flat and have sharp borders. Soft drusen tend to be larger and more amorphous with borders that are less well defined (Figures 1, 2, 8). They frequently exhibit confluence with surrounding drusen and have a more notable elevation on biomicroscopic evaluation. Exudative drusen are important as clinical markers for dry forms

of the disease, in its earliest stages. More importantly, their characteristics may serve as predictors of future risk in the development of exudative forms of AMD. Specifically, large confluent drusen (defined as greater than or equal to 125 μm in diameter with indistinct margins) and significant pigmentary changes within the retina are the major risk factors for the progression to more advanced forms of both dry and wet AMD.³⁸⁻⁴² Discussion of the increased risk for progression, need for close clinical monitoring, and role of nutrition and antioxidant supplementation is therefore imperative in this subset of patients.



Figure 10: Exudative ARMD. Subretinal hemorrhage from subfoveal choroidal neovascularization. (Photo courtesy of Lawrence A. Yannuzzi, M.D., selected from his extensive retinal images collection with the collaboration of Kong-Chan Tang, M.D.)



Figure 11: Exudative ARMD. Disciform scarring - end result of choroidal neovascularization. (Photo courtesy of Lawrence A. Yannuzzi, M.D., selected from his extensive retinal images collection with the collaboration of Kong-Chan Tang, M.D.)

Vascular Endothelial Growth Factor

Various growth factors and cytokines are implicated in the development of CNV, the most important of which is vascular endothelial growth factor (VEGF). VEGF serves as a regulator of angiogenesis and vascular permeability in embryogenesis and tumor growth and vascular protection and neuroprotection in adults. Experimental evidence supports a critical role in the maintenance of mature blood vessels with localization of VEGF and its receptors to cells of fenestrated and sinusoidal blood vessels, ocular choroid, choroid plexus, hepatocytes and other cell types.^{43,44} VEGF is produced by several different ocular cells, including glial cells, retinal pigment epithelium cells and endothelial cells.⁴⁵ The production of VEGF is usually a reaction to an ischemic environment due to disease. Experimentally, it has been demonstrated that rubeosis iri-

dis and ischemic vascular changes can be induced by VEGF injection in monkeys.^{46,47} Furthermore, inhibition of VEGF in monkeys was shown to prevent these ischemic VEGF-induced changes.⁴⁸ VEGF concentration was shown to be elevated in the ocular fluid of patients with retinal vascular ischemia secondary to diabetes and retinal vein occlusion.⁴⁹ Additional studies linked VEGF specifically to age-related macular degeneration (AMD) by demonstrating the presence of VEGF in choroidal neovascular membranes removed from patients with the disease.⁵⁰

VEGF blockade has become a mainstay therapy for the treatment of CNV in exudative AMD due to its antiangiogenic, antipermeability, and anti-inflammatory properties.^{51,52} The introduction of anti-vascular endothelial growth factor (VEGF) therapies, such as ranibizumab (Lucentis, Genentech), and bevacizumab (Avastin, Genentech) was a revolutionary advance and has been shown to significantly



improve visual acuity (VA) in many patients with choroidal neovascularization due to AMD. Vascular endothelial growth factor is central to the pathogenesis of angiogenesis and the development of CNV in AMD. Thus, its targeted inhibition by intravitreal injection has been a major breakthrough in the management of exudative AMD.

Imaging Modalities in AMD

A variety of imaging techniques and modalities are utilized in the diagnosis and management of patients with AMD. Patients with funduscopic findings of dry AMD such as drusen and RPE alterations can be monitored with serial fundus photography. Fundus photography is commonly utilized for baseline documentation and for close monitoring of progression of dry AMD. The use of fundus photography is also invaluable in educating patients on their condition. Alterations of the RPE including the identification of geographic atrophy are best demonstrated with the use of fundus autofluorescence. Fundus autofluorescence (FAF) imaging is a quick, non-invasive imaging tool for evaluating patients with nonexudative AMD (Figure 8). FAF demonstrates the topographic distribution of lipofuscin throughout the fundus, thereby providing a map of RPE integrity. A localized increase in FAF is observed in AMD patients with PED and within areas of focal hyperpigmentation.^{53,54} Geographic atrophy (GA) results in a well-demarcated area of decreased FAF corresponding to the atrophic lesion on fundus examination. Increased FAF

is often present along the margins of areas of GA.^{53,55} This increase in FAF along the margins of GA represents areas of oxidative stress or defective or altered metabolism affecting RPE integrity and might serve as markers of atrophic progression. FAF is useful for mapping an expansile creep of GA which may not be clinically apparent. This is important in reconciling the patient's symptoms and the clinical exam.

Using fundus biomicroscopy, any patient that clinically presents with findings suspicious for choroidal neovascularization should be evaluated with fluorescein angiography. These signs may include PEDs, subretinal, intraretinal or sub-RPE hemorrhage, and neurosensory detachment of the retina (Figure 13). CNV lesions may be classified by their location. They may be subfoveal (located beneath the center of the foveal avascular zone [FAZ]), juxtafoveal (posterior border of the lesion 1 to 199 microns from the center of the FAZ), or extrafoveal (posterior border of the lesion >200 microns from the center of the FAZ). Most commonly CNV presents in a subfoveal location in AMD.⁵⁶ In addition a CNV lesion can be classified based on its pattern of fluorescence into classic and occult lesion types.⁵⁶ Classic CNV is distinguished as well demarcated bright areas of intense fluorescence that appear in the early frames of the angiographic sequence, usually before 1 minute and are associated with increasing leakage in later phase of the angiogram. In contrast, occult CNV (Figures 12-14) may have two separate patterns on fluorescein angiography: fibrovascular pigment epithelial

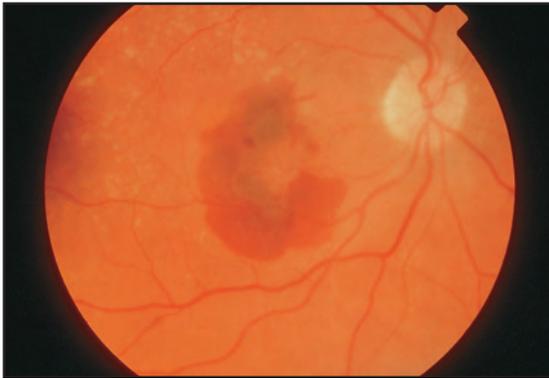


Figure 12: Exudative ARMD with Occult Choroidal Neovascularization. This is another manifestation of exudative age-related macular degeneration. Occult choroidal neovascularization with subretinal hemorrhage. (Photo courtesy of Lawrence A. Yannuzzi, M.D., selected from his extensive retinal images collection with the collaboration of Kong-Chan Tang, M.D.)

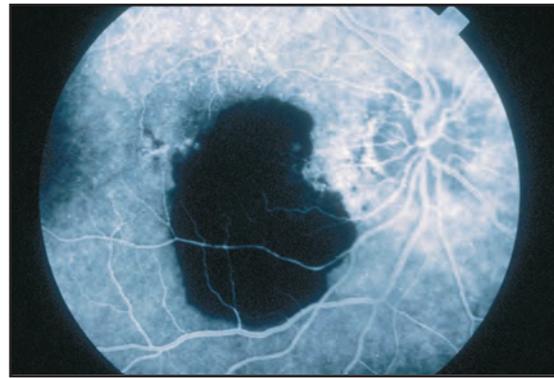


Figure 13: Exudative ARMD - Poorly Defined Choroidal Neovascularization on Fluorescein Angiography. Blockage on the fluorescein angiogram from subretinal hemorrhage. An area of juxtafoveal neovascularization is suspected in the fluorescein study. (Photo courtesy of Lawrence A. Yannuzzi, M.D., selected from his extensive retinal images collection with the collaboration of Kong-Chan Tang, M.D.)

detachment (PED) or late leakage of an undetermined source. Fibrovascular PED is characterized by irregular elevation of the RPE. It displays a stippled hyperfluorescence that typically appears later than with classic CNV. These areas demonstrate staining or leakage in the late phases and may have well or poorly defined borders. In contrast, late leakage of undetermined source is characterized by flat RPE with speckled hyperfluorescence that emerges only in the late phases of the angiogram study and that demonstrates poorly demarcated leakage. The term lesion component refers to the constituents of the lesion, which includes not only the CNV (eg, classic, occult) but also features that may obscure CNV such as thick blood, hyperpigmentation, fibrous scar, or serous PED all of which will block fluorescence.

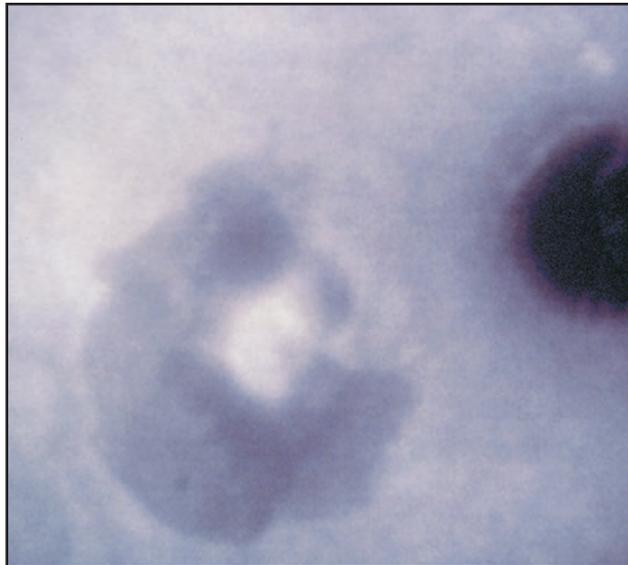


Figure 14: Exudative ARMD with Occult Neovascularization - Indocyanine Green Angiogram. Digital ICG video angiography reveals an area of neovascularization adjacent to the optic disc that could not be seen sufficiently clear on the fluorescein angiogram. (Photo courtesy of Lawrence A. Yannuzzi, M.D., selected from his extensive retinal images collection with the collaboration of Kong-Chan Tang, M.D.)



The identification of angiographic CNV lesion components was critical in clinical trials that evaluated natural history and treatment outcomes for the use of photodynamic therapy (PDT).⁵⁶⁻⁵⁸ During the PDT era, this information was invaluable in directing treatment but currently is not as crucial in clinical practice currently due to the prevalence of anti-angiogenic drugs.

Indocyanine green or ICG angiography enables enhanced imaging of the choroidal circulation. Compared to fluorescein, ICG has a higher molecular weight (775 kD vs. 375 kD) allowing for a slower rate of leakage. Due to its lipophilic and hydrophilic properties, ICG is 98% protein-bound allowing for enhanced imaging of choroidal vessels and choroidal lesions as less dye escapes from the fenestrated choroidal vasculature. In addition, ICG has peak absorption and emission wavelengths in the near infrared range (790-800 nm absorption and 830-840 nm emission).⁵⁹ Since infrared light allows for deeper penetration in tissue, it enables imaging of the choroid through the RPE.

ICG is an extremely useful diagnostic adjunct to fluorescein angiography in the presence of blood, pigment, or exudate as its wavelength allows for imaging through these entities (Figure 14). ICG can be used to detect and outline the extent of CNV, identify subtypes of occult CNV such as polypoidal choroidal vasculopathy (PCV), and masquerading diseases such as central serous chorioretinopathy (CSC).

Destro and Puliafito⁶⁰ evaluated patients with suspected choroidal neovascularization using FA and ICG. They found that ICG improved visualization of the choroidal circulation and enhanced visualization of some neovascular membranes. Yannuzzi et al⁶¹ evaluated patients with occult CNV based on FA. Using ICG, 39% of their patients were converted from occult into well-defined CNV. Guyer et al⁶² evaluated 1000 cases of CNV to describe the various types of neovascularization and determine the frequency and natural history of the various lesions. There were three types of CNV that can be observed by digital ICG videoangiography. Plaques were the most common type of lesion and overall had a poor natural history. Focal spots or hot spots were the next most common lesion and could potentially have been treated with laser photocoagulation. Combination lesions (in which both focal spots and plaques were noted) were rare. Therefore, ICG was useful in identifying lesions amenable for treatment with laser photocoagulation. In a separate study, Yannuzzi et al⁶³ evaluated patients with ICG that had evidence of occult CNV with a serous PED on FA. The authors determined that 96% of these patients had a vascularized PED and ICG was useful in the classification and identification of lesions amenable to treatment with laser photocoagulation. In addition, ICG can be used to identify and treat feeder vessels connected to the actively leaking CNV.⁶⁴ This was particularly important prior to the use of anti-VEGF medications in treating CNV as these lesions would have otherwise been considered ineligible for treatment without the use of ICG.



ICG is able to provide a more definitive diagnosis in cases of PCV. ICG clearly images the primary lesion and demonstrates dilated choroidal vessels terminating in polypoidal or aneurysmal excrescences.⁶⁵ The vessels comprising the polypoidal lesion are often more extensive than observed with clinical examination alone. In the early-phase ICG, larger PCV vessels are filled before retinal vessels and the area within and immediately surrounding the polypoidal lesions remains hypofluorescent. In the late phase, the central polypoidal lesion is hypofluorescent surrounded by an area of hyperfluorescence. This pattern of late central hyperfluorescence persists in later frames in active lesions whereas inactive lesions become hypofluorescent due to disappearance of the fluorescence from the lesions.

A subtype of AMD, retinal angiomatous proliferation or RAP, in which angiomatous proliferation originates from the retina and extends posteriorly into the subretinal space, eventually communicating in some cases with choroidal new vessels has been well documented. Based on its chronicity it can present in one of three vasogenic stages: intraretinal, subretinal, or choroidal neovascularization. ICG is invaluable in the diagnosis of RAP as it reveals a focal area of intense hyperfluorescence corresponding to the neovascularization (hot spot), and some late extension of leakage within the retina from the intraretinal neovascularization. More advanced cases can reveal a hot spot at the site of neovascularization within and beneath the retina. In cases of late RAP ICG can demonstrate a vascularized PED and the presence of a retinal-choroidal anastomosis.⁶⁶

ICG can be particularly helpful in the diagnosis of challenging cases to differentiate occult CNV from CSC.^{67,68} Patients with CSC have a focal leak on FA which can be mistaken for CNV. ICG angiography of these patients often reveals early and mid hyperfluorescence which fades in the later phases. The hyperfluorescence is believed to represent widespread changes in choroidal hyperpermeability. The extent of these choroidal angiographic changes can be greater than would be expected by clinical examination alone. By demonstrating increased choroidal hyperpermeability in patients with CSC, ICG has aided in the understanding of this disorder as primarily a choroidal vascular disorder with a secondary dysfunction of the RPE. ICG can be used to guide treatment with PDT in chronic and progressive cases of CSC. Yannuzzi et al⁶⁹ reported rapid reduction in subretinal fluid and improvement in visual acuity in cases of ICG guided PDT therapy for chronic CSC.

Optical coherence tomography (OCT) is a noninvasive imaging technique that has been used increasingly over the past several years to diagnose and monitor a variety of retinal diseases that affect the macula. Time domain OCT relies upon differential reflections of light to produce 2-dimensional cross-sections of the retina. OCT images are obtained rapidly and have a spatial resolution of approximately 8 μm . OCT is particularly useful for quantifying retinal thickness and monitoring treatment efficacy.⁷⁰ In neovascular AMD, OCT can be useful for identifying intraretinal, subretinal, or sub-RPE fluid. OCT serves as an adjunct to fluorescein angiography but is increasingly



used preferentially to assess presence of intraretinal and/or subretinal fluid in guiding the decision to retreat patients using anti-vascular endothelial growth factor agents.

Over the past 3 years spectral domain, or fourier domain OCT (SD-OCT) has been utilized to better image retinal pathology. Image acquisition times are reduced and greater resolution is obtained with SD-OCT to provide better anatomical detail and to diagnose subtle pathology. Motion artifacts can be reduced with eye tracking capability and better alignment and reproducibility of images is possible with tracking of corresponding retinal vessels. It is preferred in comparison to time domain technology in AMD patients in evaluating subtle pockets of sub-retinal or intra-retinal fluid and for more accurate retinal thickness quantification.^{71,72}

Treatment

The procedures for the management of exudative AMD are vital in preserving and often times improving central vision. These procedures include but are not limited to intravitreal injection of an anti-VEGF (vascular endothelial growth factor) drug, laser photocoagulation, photodynamic therapy, photodynamic therapy with intravitreal steroid, and surgical translocation of the macula. Multiple treatments may be required to achieve complete resolution of the leakage from CNV, and therefore patients are monitored closely for treatment response and for signs

of subsequent leakage. The benefits of each treatment must be weighed against potential complications inherent to each treatment modality. Each of the possible available treatment options are limited in their effectiveness by the repeated need for intervention and the individual variability of tissue response to treatment.

Precautions for Higher Risk Patients

Persons at higher risk of macular degeneration with genetic susceptibility should see their ophthalmologist regularly. If indicated, they should have fluorescein angiography and optical coherence tomography. They can perform self assessment weekly or even daily using an Amsler grid or merely by looking at the same test object like a clock illuminated in the same way and at the same distance. Each eye should be tested separately. At the first sign of any blurring, distortion, or decreased acuity, the person should return to the ophthalmologist promptly for a check-up. Self-monitoring by patients is critical in the early detection and treatment of exudative AMD as visual symptomatology may be subtle and treatment response is greater for those lesions with early detection. This opportunity is often missed when these patients are slow to realize that their vision is somewhat reduced in one eye. Unfortunately in these instances the macular degeneration is often too advanced on presentation resulting in a less effective treatment response.



Prevention of ARMD

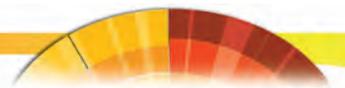
As previously mentioned, a great deal of current research concerns more specific identification of patients who are at the greatest risk of developing macular degeneration so that precautions can be taken as outlined above. Other approaches are being considered, particularly in relation to nutrition, modification of cardiovascular risk factors and smoking cessation.

Nutritional Intervention

The Age-Related Eye Disease Study, an 11-center double-masked clinical trial enrolled 4753 patients to evaluate the effect of high-dose micronutrient supplementation consisting of antioxidants and vitamins (500 mg vitamin C, 400 IU vitamin E, and 15 mg beta carotene) and zinc (80 mg zinc oxide and 2 mg of cupric oxide to prevent zinc-induced anemia) on AMD. The recommendations were for patients with extensive intermediate size drusen, at least 1 large druse, noncentral geographic atrophy in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye, and without contraindications such as smoking, to supplement their diet with antioxidants and zinc.⁷³ Higher dietary intake of lutein/zeaxanthin was independently associated with decreased likelihood of having exudative AMD, geographic atrophy, and large or extensive intermediate drusen.⁷⁴ Recently, a multicenter clinic-based prospective cohort

study from a clinical trial including Age-Related Eye Disease Study (AREDS) participants was conducted to study the association of dietary omega-3 long-chain polyunsaturated fatty acids and fish intake with incident exudative AMD and central geographic atrophy. Dietary omega-3 long-chain polyunsaturated fatty acid intake was associated with a decreased risk of progression from bilateral drusen to central geographic atrophy.⁷⁵ The current recommendation for patients with bilateral large drusen and those with advanced AMD in 1 eye is to take an AREDS-type supplementation. Caution should be exercised by smokers however, as they should avoid beta-carotene for the increased risk of lung carcinoma.

A retrospective epidemiologic study has found that people who eat large amounts of leafy green vegetables, particularly spinach and kale, 4 to 6 times per week seem to have a lower incidence of macular degeneration. Whether this diet would actually reduce the incidence of macular degeneration in people who are at increased genetic risk, no one knows for sure. But eating a well-balanced diet may offer some protection. Whether to take vitamins and mineral supplements at this time is an individual decision. Overall the modification of cardiovascular risk factors along with smoking cessation should be stressed to susceptible patients. Smoking has a harmful effect on many parts of the body, and confers an increased risk of macular degeneration.



AREDS 2 is a multi-center randomized trial currently underway designed to assess the effects of oral supplementation of high doses of macular xanthophylls (lutein and zeaxanthin) and omega-3 long-chain polyunsaturated fatty acids (DHA and EPA) on the progression to advanced AMD. Enrolled participants had either bilateral large drusen (>125 microns) or large drusen in one eye and advanced AMD in the fellow eye. Participants were followed for a minimum of 5 years and were offered additional treatment with the original AREDS formulation and 3 variations of this formula including no beta-carotene, lower amounts of zinc, and no beta-carotene and lower amounts of zinc. The results of this clinical trial are currently pending at the time of this publication.

Conclusion

AMD is a leading cause of vision loss in the elderly worldwide. Great strides have recently been made in the research arena with the enhanced imaging capability afforded by OCT, the identification of a variety of genetic markers and the development of effective medications specifically targeting VEGF inhibition. As the proportion of the elderly population continues to increase in the United States, further developments in the early identification and treatment of this disorder will be critical as will preventive measures determined through clinical trials. These measures will inevitably help to improve the visual outcomes of those affected by this disorder and hold great promise for the future.

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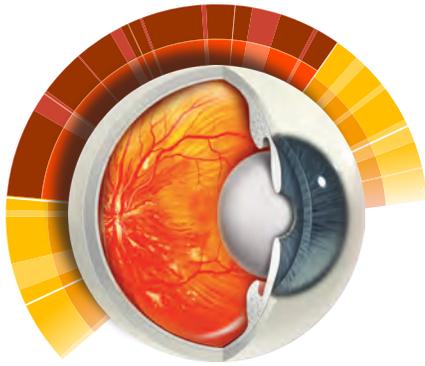
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Highlights in the Management of Age-Related Macular Degeneration

STANISLAO RIZZO, MD.,
FRANCESCO FARALDI, MD.,
EMANUELE DI BARTOLO, MD.,
MARIA MADDALENA RABBIONE, MD.

INTRODUCTION

Age related diseases like Alzheimer's Disease and age-related macular degeneration (AMD) are, by definition, chronic late-onset disorders with peculiar histopathological and clinical hallmarks. However, drusen and retinal pigment epithelium (RPE) hyper/hypopigmentation, markers of age related maculopathy, as well as Alzheimer's neurofibrillary tangles, can be found to a lesser extent in aged normal subjects.^{1,2} Susceptibility to develop these forms of deviations from normal ageing depends on a growing amount of genetic and environmental risk factors. Any of these factors and related pathophysiological modifications but age, is now looked at as the possible target of future therapies of these diseases and in particular AMD.

Genetic susceptibility is fundamental: population-based studies implicate a familial component in the disease's pathogenesis, as indicated by studies of twins.³ Due to the multifactorial nature of the disease, only recently several genome-wide linkage analyses and case-control studies have identified different AMD-related gene variants, including complement factor H (CFH) polymorphisms at chromosome 1q31, LOC387715 and HtrA serine peptidase 1 (HTRA1) promoter at chromosome 10q26.^{4,5} The strongest association with the risk for developing all stages of age-related macular degeneration has been demonstrated for the gene encoding CFH.⁶⁻⁹ CFH is a regulator of the complement system of innate immunity by inhibiting the activation of C3 to C3a and C3b and by inactivating existing C3b, interfering with the progression



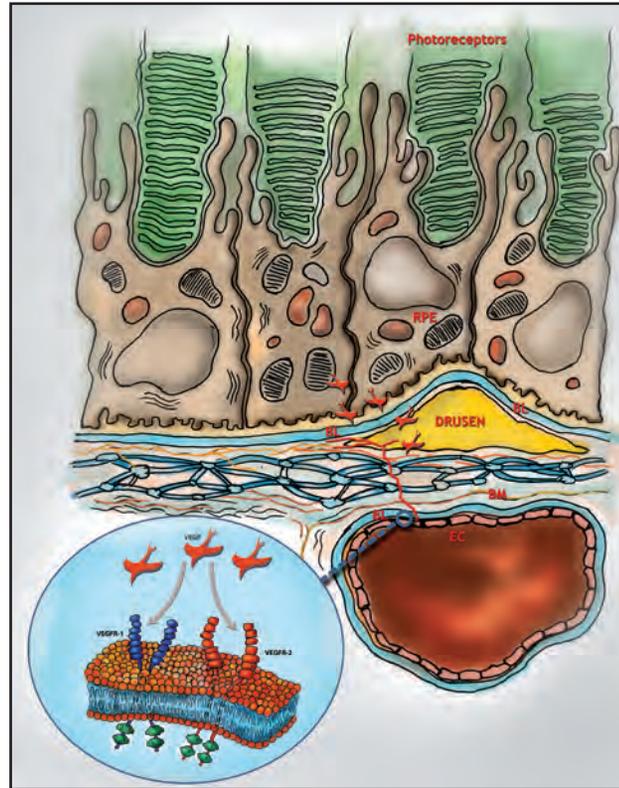
of the entire complement cascade.¹⁰ Several sequence variations in the region of the gene of CFH show a strong association with AMD susceptibility.¹¹ Particularly, the association with AMD development of the single nucleotide tyrosine-histidine polymorphism in which a neutral tyrosine is replaced by a positively charged histidine (Y402H-encoding CFH variant) has been now reported and replicated in multiple samples;¹² individuals homozygous for the CFH Y402H polymorphism showed a 48% risk of developing late AMD by age 95 compared to 22% for non carriers being the potential causal factor in more than 50% of all AMD cases.¹³

Moreover, the association between AMD and HTRA1, LOC387715 and complement components 2 and 3 (C2, C3) variants, independent of the CFH polymorphism, have been recently described.^{5,14-17} Multiple environmental risk factors have been determined by case-controlled population studies: body mass index, smoking, sunlight exposure.^{18,19} The most important factor (associated with at least a 2-fold increased risk) seems to be cigarette smoking and a direct association between the risk of developing advanced age-related macular degeneration and the number of smoked cigarettes has been documented.^{20,21}

The etiology and pathogenesis of AMD remain largely unclear and a complex interplay of these genetic and environmental factors is thought to exist; recent reports show that the combination of genetic risk (CFH polymorphism) and smoking can significantly exceed the sum of the independent risk factors.^{13,22} Diverse cellular processes have been implicated in AMD pathogenesis, including

oxidative stress, inflammation, altered cholesterol metabolism and/or impaired function of the RPE and local or systemic factors are involved in the disease evolution to the advanced atrophic or neovascular complications.^{23,24} Histopathological and biochemical evidences point the interest on mechanisms of hyper accumulation of oxidative byproducts and abnormal activation of the inflammatory cascade.^{25,26} The retina has a high oxygen consumption related to photoreceptor visual function and RPE activity under a continuous high exposure of light with a chronic oxidative damage to retinal and RPE cell structures and DNA.²⁷ Products of cell components' oxidation are constituents of drusen. Drusen are deposits of neutral lipids, with esterified and nonesterified cholesterol, carbohydrates, zinc, and at least 120 different proteins, including apolipoproteins (e.g., apoE, apoB) (Figure 1); hallmarks of oxidative stress are carboxyethyl pyrrole (CEP) adducts, oxidative protein modifications generated from docosahexaenoate (DHA)-containing lipids, and crosslinked species of proteins TIMP3 and vitronectin.²⁸ A chronic inflammatory process with direct and bystander cell damage attributable to a complement-mediated attack exacerbating the effect of primitive pathogenic stimuli is supported by several observations. Proteins involved with inflammation (e.g., amyloid-b, immunoglobulin light chains, factor X, C5, and C5b complex) are normal constituents of drusen.²⁹ Mononuclear phagocyte series cells and giant cells with internalized pigment clumps are present in atrophic lesions.³⁰ Interestingly, *in vitro* findings have shown that the RPE cells under oxidative stress lose the ability to suppress complement activation on their surface and synthesize the proangiogenic mediator Vascular Endothelial Growth Factor

Figure 1: Drusen are markers of age related maculopathy. Vascular Endothelial growth Factor (VEGF) is one of the soluble modulators of ocular angiogenesis. (RPE: retinal pigment epithelium. BL: Basal lamina. BM: Bruch's membrane. EC: Endothelial cells. VEGFR: VEGF receptors).



(VEGF), possibly unbalancing the normal equilibrium between the proangiogenic VEGF and the anti-angiogenic neurotrophic and neuroprotective effects of Pigment Epithelial-Derived Factor (PEDF) (Figure 1)²⁵.

VEGF is one of the soluble modulators of ocular angiogenesis and, like Platelet derived Growth Factor (PDGF), Fibroblast Growth Factors (FGFs) 1 and 2 and Transforming Growth Factor beta, is not expressed at detectable levels in normal RPE. These factors have been described in choroidal neovascularization (CNV) in several cell types, such as neuroretinal cells, RPE cells, endothelial cells, macrophages and fibroblasts.³¹⁻³³

Experimental and clinical studies have demonstrated VEGF as critical for promoting CNV. The VEGF is a family of several heparin binding glycoproteins: VEGF-A (after referred to as VEGF) is involved in many processes implicating angiogenesis both in normal and in pathologic conditions. VEGF exists as 4 splice variants with a different number of amino acids: VEGF121, VEGF165, VEGF189 and VEGF286 and in a proteolytic cleavage product: VEGF110.³⁴ Among these, VEGF165 seems to be the most biologically active and the principal responsible for pathologic ocular neovascularization.³⁵ Soluble factors are not the only players involved in ocular neovascularization, a highly complex process



modulated also by non soluble factors like extracellular matrix elements and intercellular adhesion molecules.

A compelling amount of research informations is every day shedding light on mechanisms of AMD early and late phases while new therapeutic strategies and new molecules with therapeutic potential in halting a step of the AMD degenerative process are investigated.

DRY AMD THERAPY

The Age Related Disease Study (AREDS) established that the dietary supplementation with antioxidant (vitamin C 500 mg, vitamin E 400IU, b-carotene 15 mg) and zinc (zinc, 80 mg, as zinc oxide and copper, 2 mg, as cupric oxide) can reduce the risk of developing advanced age-related macular degeneration by as much as 25% over 5 years in subjects with at least moderate risk of age-related macular degeneration. This was accompanied by a 19% reduction in the risk of moderate vision loss (three or more ETDRS lines) at 5 years. The visual benefit is greatest, and was statistically significant in people with late AMD in one eye and early AMD in the other. There is no benefit in patients with no signs of AMD or those with bilateral, advanced AMD. These high doses of zinc and anti-oxidants cannot be achieved from diet alone.³⁶ Beta-carotene is not recommended for smokers as it has been shown to increase the risk of lung cancer.³⁷

The protective role of lutein and its isomer zeaxantin as well as the intake of unsaturated fatty acid like docosahexaenoic acid (DHA) are still under evaluation.^{38,39}

Pharmacogenetic studies are now evaluating interactions between genetic variants and treatment response. Klein et al. have shown a treatment interaction between the CFH Y402H genotype and supplementation with antioxidants plus zinc on 876 patients in the AREDS category 3 and 4 at high risk of developing advanced AMD. Moreover, an interaction was observed in the groups taking zinc vs the groups taking no zinc, but not in groups taking antioxidants compared with those taking no antioxidants. There were no significant treatment interactions observed with LOC387715/ARMS2.⁴⁰ Joint effect of demographic environmental and six genetic variants has recently allowed the formulation of a prediction model for progression of AMD above and beyond the ocular signs and the only significant interaction between genetic variants and treatment was found with CFH Y402H polymorphism.¹²

WET AMD TREATMENT OPTIONS

Angioocclusive therapies. Until 2000, **thermal laser photocoagulation** was used to obliterate neovascularization. Macular Photocoagulation Study Group demonstrated that laser reduces the risk of severe visual loss for eyes with symptomatic choroidal neovascular membrane at least 200 μm from the center of the Foveal Avascular Zone (FAZ). However, only 13-26% of patients with exudative neovascular AMD fit the criteria for argon laser treatment and those undergoing laser treatment experienced CNV persistence or recurrence in 50% of cases.⁴¹ Subfoveal treatment usually resulted in immediate, significant visual acuity loss related to RPE and retinal

damage.⁴² Recently, a Cochrane systematic review concluded that laser photocoagulation slows progression of neovascularization in non-subfoveal lesions compared with observation alone.⁴³

Photodynamic therapy (PDT) with verteporfin, a lipophylic dye administered intravenously, was the first pharmacologic treatment for wet AMD to receive regulatory approval, becoming the standard of care for the treatment of neovascular AMD.⁴⁴ Verteporfin PDT's clinical efficacy and safety has been demonstrated in several, multi-center, double-masked, randomized placebo-controlled clinical studies. In the two studies known as TAP investigation (Treatment of AMD with PDT), verteporfin treatment significantly prevented moderate vision loss in patients with predominantly classic lesions. At 12 months, 61% of the treated patients versus 38% of the placebo-treated patients lost less than 15 ETDRS letters of best corrected visual acuity. In the subgroup analyses, patients with purely occult lesions showed a nonstatistically significant trend toward benefit, and patients with minimally classic lesions did not show any benefit.⁴⁵ According to guidelines for the management of CNV published by European Medicine Agency and US Food and Drug Administration, PDT is indicated for patients with predominantly classic lesions secondary to AMD (50% or more of the lesion consists of classical choroidal neovascularization). The mechanism of action of PDT is not fully understood. It is thought that verteporfin accumulates preferentially in the neovasculture because of the increased uptake of low density lipoproteins (LDL) and expression of LDL receptors, in rapidly proliferating cells⁴⁶

and is activated by a non-thermal laser resulting in generation of reactive oxygen species causing endothelial cell changes leading to the occlusion of choroidal neovessels.⁴⁷ However, several clinical and research evidences have demonstrated a lack of selectivity resulting in transient occlusion of the normal choriocapillaris with fluorangiographic and indocyanin green angiography evidence of hypoperfusion. Histology has shown a damage of the normal choroidal endothelial cells and neovessels formation within the CNV after PDT possibly related to the increased expression of VEGF in PDT treated areas.⁴⁸ Recurrence of CNV and loss of vision are experienced by many of the treated patients. Therefore still debated are the treatment regimen and the light dose (reduced and half fluence) to be adopted in order to reduce the hypoperfusion of the normal choroid and the reported damage to the endothelial cells of the choriocapillaris and RPE in order to obtain a truly selective damage to the CNV.⁴⁹

Alternative angioocclusive therapies include transpupillary thermotherapy,⁵⁰ radiotherapy⁵¹ and feeder vessel treatment of AMD-related CNV.⁵²

Anti-VEGF therapies. Anti-VEGF therapies inhibit blood vessel growth and leakage of CNV. To this date, two molecules have been approved by Food and Drug Administration: an aptamer (pegaptanib sodium; Macugen, OSI/Pfizer) and an antibody fragment (ranibizumab; Lucentis, Genentech). These molecules prevent the interaction between VEGF and VEGF receptors (VEGF-R) binding VEGF itself with high selectivity (Figure 2).

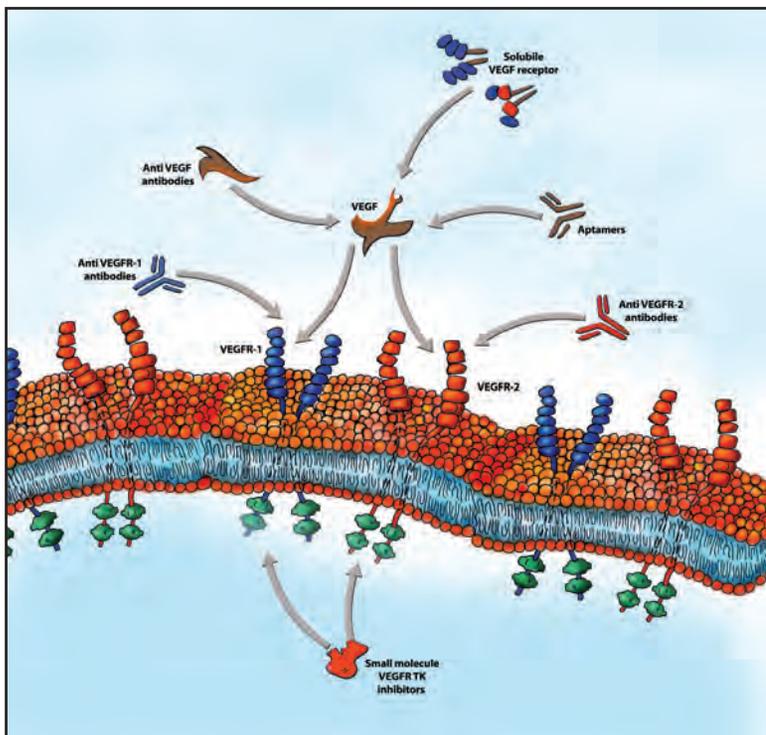


Figure 2: Anti-VEGF inhibitors can act directly binding the VEGF (aptamers, anti-VEGF antibodies and soluble VEGF receptors). VEGF inhibition can otherwise be obtained inactivating the VEGF receptors (VEGFR) or through the inhibition of the intracellular kinases (VEGFR TK) blocking the intracellular cascade.

Pegaptanib sodium is an RNA oligonucleotide aptamer. The molecule has been modified at 2 hydroxyle groups of its bases to render it less susceptible to hydrolysis and conjugated to a polyethylene glycol group to increase the half-life. Pegaptanib binds specifically to VEGF 165.⁵³ Two phase II/III concurrent, prospective, randomized, multicenter, double-masked, sham-controlled, dose-ranging (0.3,1,3 mg) clinical trials, VEGF Inhibition Study in Ocular Neovascularization (VISION), were published in 2004.⁵⁴ At 54 weeks, 70% of patients in the 0.3 mg group met the primary end point (losing fewer than 15 letters at ETDRS chart), 71% in the 1 mg group, 65% in 3 mg group and 55% in the sham group. The 0.3 mg administered every 6 weeks was chosen as the lowest

efficacious dose. On average, patients in all groups still lose vision, ranging from a loss of 6 letters in the 1.0 mg group to 15 letters in the control group. In subgroup analysis, pegaptanib was effective across all CNV types. These results were confirmed at the end of the second year of follow-up, in which mean Visual Acuity (VA) of patients maintained with 0.3 mg every 6 weeks remained stable.⁵⁵ Systemic potential adverse events of anti-VEGF drugs (hypertension, proteinuria and peripheral thromboembolic events) didn't occur with greater frequency in patients who received pegaptanib sodium, local adverse events were transient and attributed to the injection procedure, as confirmed at the end of the third year of follow-up.⁵⁶

Ranibizumab is a humanized monoclonal antibody fragment, produced in *Escherichia coli* by recombinant DNA technology. It binds with high affinity to all VEGF isoforms. It results from the insertion of murine anti-VEGF-A complementary-determining regions (CDRs) into a human IgG1 framework.⁵⁷ The two major phase 3 clinical prospective, randomized, double-blind, sham-controlled trials for ranibizumab are known as MARINA and ANCHOR. The MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration) is a study on safety and efficacy of intravitreal injections of ranibizumab administered every four weeks in patients with minimally classic and occult CNV associated with AMD. The study met its primary endpoint at 12 months when 94.5% of the patients receiving ranibizumab 0.3 mg and 94.6% of those receiving 0.5 mg had lost fewer than 15 letters from baseline, as compared with 62.2% in the sham-injection group. Furthermore, this is the first wet AMD treatment in which not only stabilization but also an increase of visual acuity was observed. At 12 and 24 months, approximately one quarter of patients treated with 0.3 mg of ranibizumab and one third of patients treated with 0.5 mg gained 15 or more letters, as compared with 5% or less of those in the sham-injection group. A subgroup analysis revealed that the most important predictors of visual acuity outcomes were baseline visual acuity score, CNV lesion size, and age.⁵⁸ In the ANCHOR study (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration) eligible patients were

randomly assigned in a 1:1:1 ratio to receive either 0.3 or 0.5 mg of ranibizumab plus sham verteporfin therapy or sham intravitreal injections plus active verteporfin therapy. All end points with respect to visual acuity in the study eye at 12 months favored ranibizumab treatment over verteporfin therapy. With respect to the primary efficacy end point, 94.3% of patients in the 0.3 mg group and 96.4% in the 0.5 mg group lost fewer than 15 letters from baseline visual acuity, as compared with 64.3% in the verteporfin. In addition, the proportion of patients whose visual acuity improved from baseline by 15 or more letters was significantly greater among those receiving ranibizumab treatment (35.7% in the 0.3 mg group and 40.3% in the 0.5 mg group, as compared with 5.6% in the verteporfin group; $P < 0.001$ for each comparison). In summary, the ANCHOR study showed that ranibizumab administered monthly by intravitreal injection was superior in efficacy to photodynamic therapy with verteporfin in patients with subfoveal, predominantly classic choroidal neovascularization associated with age-related macular degeneration. The 2-year results confirmed the visual acuity gain maintenance in both ranibizumab groups.⁵⁹ Intravitreal injections of ranibizumab were associated with a low rate of serious ocular adverse events: most common were presumed endophthalmitis and severe intraocular inflammation (reported in less than 0.1% of pooled ranibizumab injections). Patients treated with a 0.5 mg dose had a higher rate of arterial thromboembolic events (mostly with a history of stroke or arrhythmia) than did those who received a 0.3 mg dose or control cases but the difference was not statistically significant.⁶⁰



Subsequent studies were designed to determine whether a less frequent ranibizumab dosing schedule would prevent loss of visual acuity in patients with AMD reducing the treatment burden for the patients. In the phase IIIb, multicenter, randomized, double-masked PIER trial (Randomized, Double-Masked, Sham-Controlled Trial of Ranibizumab for Neovascular Age-related Macular Degeneration), based on the evidence that pharmacodynamic activity of ranibizumab may last 90 days, patients received monthly injections for the first 3 months and then once every three months. While the efficacy in preserving from loss of visual acuity was maintained (-1.6 and -0.2 letters in the ranibizumab 0.3 mg and 0.5 mg groups vs -16.3 in the sham group), the vision gain obtained after 3 months was not observed at 12 months.⁶¹

The PrONTO (Prospective Optical coherence tomography imaging of patients with neovascular AMD treated with intra-ocular ranibizumab -Lucentis-) study was a 2-year, open-label, prospective, single center clinical study designed to investigate the efficacy, durability and safety of a variable-dosing regimen with intravitreal ranibizumab, OCT-guided, in patients with neovascular AMD. Intravitreal injections of ranibizumab were administered to all patients at baseline, month 1, and month 2. Additional reinjections were given if any of the following changes were observed by the evaluating physician during the first year of the study: VA loss of at least 5 letters with OCT evidence of fluid in the macula, an increase in OCT central retinal thickness of at least 100 μm , new macular hemorrhage, new area of classic CNV, or

evidence of persistent fluid on OCT one month after the previous injection. During the second year, an amendment to the study changed the retreatment criteria to include any qualitative change in the appearance of the OCT images that suggested recurrence of fluid in the macula (e.g. appearance of retinal cysts, subretinal fluid, enlargement of a pigment epithelial detachment). VA improved by 11.1 letters at 24 months with a 95% CI ranging from 7 letters to 15.2 letters, suggesting results comparable with the phase III trial results. Whereas patients in the MARINA and ANCHOR trials received 24 injections over 24 months, the patients in the PrONTO Study received an average of just 9.9 injections with a median of 9.0 injections. 97.5% of patients avoided a 15-letter VA decrease, 43% of patients gained at least 15 letters of VA, 78% of patients didn't lose any letters. The PrONTO Study suggests that VA outcomes with an OCT-guided treatment with ranibizumab seem to be comparable with the results obtained with monthly injections.⁶²

Current strategies of treatment with ranibizumab will be revisited according to prospective, randomized, double-masked ongoing trial with the aim of reducing the number treatment with visual acuity results comparable to monthly fixed dosing regimen.⁶⁰

Bevacizumab (Avastin). is a humanized monoclonal antibody binding all isoforms of VEGF. It was designed for intravenous administration and approved in 2004 for the treatment of metastatic colorectal cancer.⁶³ The first use of intravitreal bevacizumab for wet AMD was reported in a single case in 2005.⁶⁴ Since then, the use of intravitreal

bevacizumab as an off label treatment for neovascular AMD has become widespread. Several small, uncontrolled retrospective and prospective studies of intravitreal bevacizumab in neovascular AMD have been published.^{65,66} Recently published results of a prospective study on 51 eyes of 51 patients treated with 2.5 intravitreal bevacizumab over 24 months suggest that this treatment is safe (one patient required surgery for instable angina and no ocular adverse event were reported) and efficacious: mean visual acuity improved significantly from 45.7 letters at baseline to 54.3 letters at 24 months, 92.2% lost fewer than 15 letters.⁶⁷ Debated is the minimum efficacious dose: dose ranging in published studies is 1 - 2.5 mg, although recently Arevalo suggested that 1.25 mg may have equal efficacy of higher doses.⁶⁸ Adverse events reported in a registry compiling adverse experiences of 7113 injections⁶⁹ included ocular complications (more frequent bacterial endophthalmitis in 0.16% and retinal detachments in 0.16%) and systemic complications (acute elevation of blood pressure in 0.59%, cerebrovascular accidents in 0.5%, myocardial infarction in 0.45 and death in 0.4%). Randomized, controlled trials comparing bevacizumab with approved therapies are still ongoing.⁷⁰

Combination therapies. An ideal therapy for AMD, taking into account the multifactorial pathogenesis, would eradicate pre-existing neovessels as well as reduce inflammation and VEGF expression to prevent further CNV growth. No single therapy possesses all of these action modalities. Nonetheless, intravitreal anti-VEGF monotherapies must be frequently administered for a prolonged period of time to maintain the VA benefit

and recent clinical data indicate a possible resistance and tolerance to both ranibizumab and bevacizumab.⁷¹

Currently, combinations of two or three therapies, compared with anti-VEGF monotherapy are being tested for their ability to reduce the intervention rate with equivalent efficacy and safety results. These include the combination in various ways of PDT, radiation therapy, pegaptanib, ranibizumab, bevacizumab, triamcinolone, dexamethasone.

Large case series have demonstrated the advantages of combining standard PDT and high dose intravitreal triamcinolone but serious adverse complications have been reported.⁷²⁻⁷⁴

Efficacy of standard PDT and bevacizumab 1,25 mg (within 14 days) combination treatment has been recently examined in a large retrospective multicenter case series. With one combination treatment at baseline and a mean of 0.6 additional verteporfin PDT retreatments and 2.0 bevacizumab retreatments over a mean follow-up period of 15.0 months, after 12 months (701 cases) 82% of patients had stable or improved vision (loss of <3 lines or a gain in VA), 36% improved by > or =3 lines, and 17% improved by > or =6 lines with a mean vision gain of approximately 1.2 lines of VA from baseline. Patients who were treatment naïve gained significantly more compared with those who had been previously treated.⁷⁵

Augustin et al treated 104 eyes, with reduced light dose (42 J/cm) of PDT by



verteporfin, 800 μg of dexamethasone and 1.5 mg of bevacizumab intravitreal injection after 16 hours. Five patients received a second PDT and 18 patients had a second bevacizumab injection in 40 weeks of follow-up (range, 22-60 weeks) with a mean visual acuity improvement of 1.8 lines, with 39.4% gaining three or more lines and 3.8% losing three or more lines.⁷⁶ In Yip series of consecutive cases treated with standard fluence PDT and intravitreal injection within one hour of 4mg of triamcinolone and 1.25 mg of bevacizumab, 78% achieved CNV eradication, and 61% achieved visual stabilization at 6 months, with 30% and 28% gaining three or more lines at 3 and 6 months respectively.⁷⁷ In a recent retrospective cases serie with 13.7 months mean follow-up, same day triple therapy with reduced fluence photodynamic therapy (25 J/cm), intravitreal dexamethasone (200 microg), and intravitreal bevacizumab (1.25 mg) gave good results particularly in naive treated patients.⁷⁸

International multicenter double-masked placebo controlled trials are currently ongoing with the aim of better understanding advantages and disadvantages of combination therapies with currently usable drugs.

SURGICAL TREATMENT OF WET AMD

Limits of current therapies of AMD are well known: necessity of repeated injections over several months, high costs, poor patient compliance, organizational problems for medical facilities, and in some cases, treatment failures. Alternative therapies are therefore still under investigation.

Few surgical options have been proposed, for the time being, confined to advanced cases, non-responders to other treatments and treatment failures often complicated by large hemorrhages.

CNV excision. The Submacular Surgery Trial (SST) has shown that subretinal neovascular membrane excision is not advantageous in AMD.^{79,80} Bottoni and colleagues⁸¹ have further shown that the affected part of the RPE increases, on average, 19.5 times compared to the affected area before surgery.

Therefore, most surgeons have moved to complex surgical procedures enabling a rotation of the macular neural retina over a healthy RPE area.

Macular Translocation. In Macular Translocation (MT) a iatrogenic retinal detachment is induced, followed by the removal of the neovascular membrane and relocation of the fovea to an unaffected part of the RPE and choroid.⁸²⁻⁸⁴

In full macular translocation (FMT) or 360° translocation, a complete peripheral retinotomy enables the rotation of the whole retina allowing a wide displacement of the fovea (usually upwards).⁸⁵⁻⁸⁹

In Limited Macular Translocation (LMT) the fovea is moved by punctate retinotomies once a local detachment of the posterior pole is induced, with or without a scleral shortening from the outside ('infecting' or 'outfolding').⁸⁹⁻⁹³

FMT allows to move the fovea up to 3300 micron or more compared to little more than 1000 micron in LMT, and is thus more indicated in more advanced CNV cases.⁹⁴ MT surgical procedure is complex, requires a highly experienced surgeon, and the complications are numerous, both intraoperatively (retinal ruptures, ocular hypotony, macular folds and vitreous, retinal and choroidal hemorrhages) and postoperatively (hemorrhages, relapse of the neovascularization, torsional diplopia, ocular hypotony, macular holes and retinal detachment with PVR).⁷⁹⁻⁸⁷

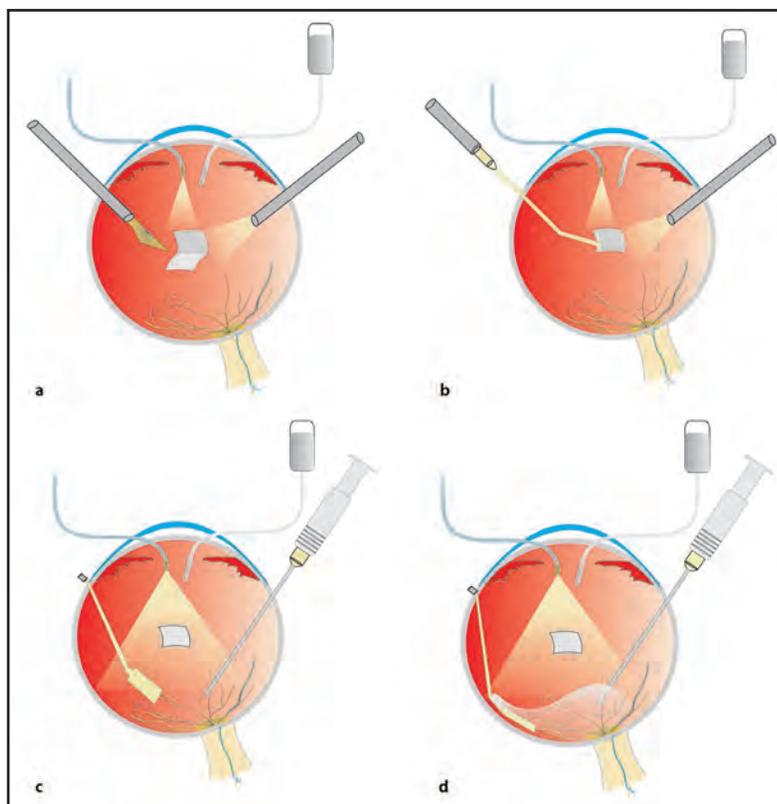


Figure 3: Autologous transplantation of a peripheral RPE-choroid patch that is inserted underneath the macula following surgical CNV excision.

Presently, only limited case studies are reported and a recent analysis published on the Cochrane Database of Systematic Review⁹⁵ concludes that at the moment there is not sufficient scientific evidence, based on randomized and controlled trials, to extend the use of this surgical procedure.

The most encouraging results have been achieved by small studies comparing the efficacy of LMT and PDT in myopic patients: in the LMT group 55% of the patients showed an increase of 3 or more lines in BCVA and 60% had an improvement of at least 5 letters compared to 10% and 40% in the PDT group.⁹⁶

Autologous pigment epithelium transplant. The necessity of restoring a healthy RPE underneath the foveal area has led to autologous transplantation of a peripheral RPE-choroid patch that is inserted underneath the macula following surgical CNV excision (Figure 3). The transplanted tissue grafts onto the new area in most cases and patch vitality can be shown by angiography and autofluorescence (AF). Revascularization of the transplanted RPE and choroid allows a functional improvement in some cases.



However, the rate of complications, which may be serious, leading to more interventions, appears significant and can be higher than 60%.⁹⁷⁻⁹⁹

A recent study¹⁰⁰ compares the long-term results of MT and RPE transplantation (patch graft, PG) and shows that after 3-year follow-up the MT group maintained functional results that were superior to the PG group showing a progressive loss of retinal function. The authors attribute this effect to major surgical trauma and to the failed perfusion of the part transplanted in the first few days postop with a permanent damage to the foveal receptors.

Relocation and drainage of subretinal hemorrhages. The onset of a massive subretinal hemorrhage is one of the most serious complications in patients with wet AMD, and causes a sudden and substantial vision loss. Occasionally, visual acuity is recovered spontaneously but generally the prognosis is negative. Experimental studies demonstrate that permanent changes of the retina start to develop 24 hours after the bleeding, with loss of photoreceptors due to mechanical, metabolic and toxic damage.

Thus, in these cases an early relocation or drainage of the hemorrhage is fundamental for a better functional prognosis. A gas tamponade with Sulfur Hexafluoride (SF₆) with or without a Recombinant Tissue Plasminogen Activator (r-TPA) injection seems advisable for achieving better vision. Nevertheless, the penetration of intravitreally injected r-TPA through the retina and the necessity of injection in the subretinal space are still debated.

In a meta-analysis of the results achieved by various surgical procedures for wet AMD, Falkner and colleagues¹⁰¹ compared SST data with VA outcomes of MT, RPE transplantation and removal of major subretinal hemorrhages, using data from 88 studies published between 1992 and 2004. The Authors concluded that removal of neovascularization, macular translocation and RPE transplantation, show a rate of improvement of 2 ETDRS lines or more similar to the percent of cases with VA decline of 2 or more ETDRS lines with high a frequency of complications (50-80%). Subretinal hemorrhage removal show a significant favorable effect on functional prognosis: 62% improvement versus 13% decline, and a 37% rate of complications.

Epiretinal brachytherapy. Attempts to use external radiation of the posterior pole to inhibit or slow down the proliferation of subretinal neovascular vessels have produced disappointing results both in terms of efficacy and safety because of radiation effects on the adjacent tissues (lens, optic nerve, ocular adnexa) and on the retina itself (radiation retinopathy).

Recently, a new epiretinal brachytherapy procedure was developed: during a vitrectomy, a probe with strontium-90 beta isotope (Neovista®) allows to exclusively radiate the macular area to a depth of only 3 mm and covering an area of 5 mm in diameter with a limited application of 24 Gy (Figure 4). The use of epiretinal brachytherapy combined with intravitreal anti-VEGF agents injections has shown promising safety and efficacy profiles in pilot studies. In a recent report on 34 patients with follow-up of 12 months, 96% of

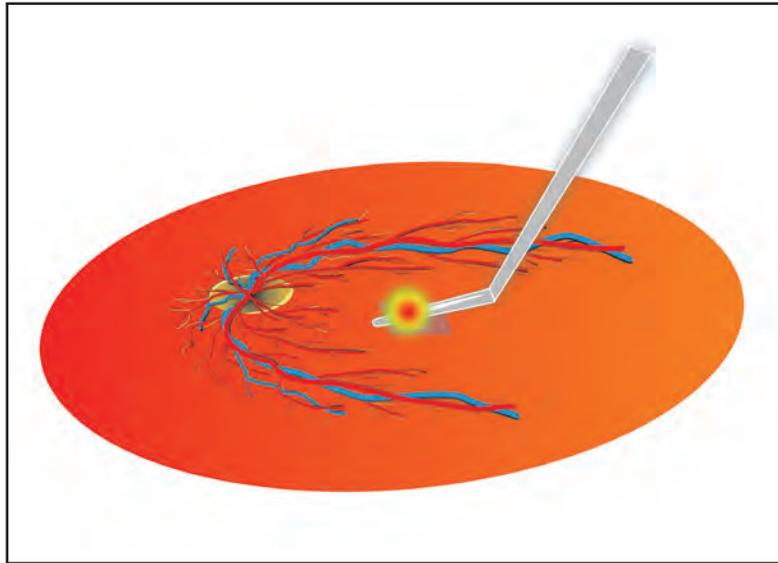


Figure 4: Epiretinal brachytherapy: a probe with strontium-90 beta isotope (Neovista®) allows to exclusively radiate the macular area.

patients lost 15 or fewer letters, with a mean VA increase at the end of the follow-up of 10.7 letters.¹⁰² Furthermore, at the end of the follow-up there was no evidence of radiation retinopathy but an increase of the crystalline opacity, possibly related to the surgical procedure. Multicenter randomized and controlled studies are under way, aiming to compare the efficacy of this new procedure with the standard of care therapies with anti-VEGF agents.

Suprachoroidal infusion of drugs. The therapeutic effect of pharmacological combinations may be amplified by administration in the suprachoroidal space thanks to a purposely conceived microcatheter (iTrack TM-iScience

Interventional Corp., Menlo Park, CA) while reducing the possible systemic absorption of these drugs.

Preliminary studies on an animal model show that the microcatheter allows the injection of triamcinolone acetonide in the posterior suprachoroidal space with a low incidence of complications, and although the drug remains in the injection spot for at least 120 days, the systemic levels are minimal.¹⁰³

A pilot study is ongoing to establish the safety and feasibility of suprachoroidal administration of 4mg (0.16ml) of bevacizumab and 4mg (0.1ml) of triamcinolone acetonide through the ophthalmic microcatheter inserted via an

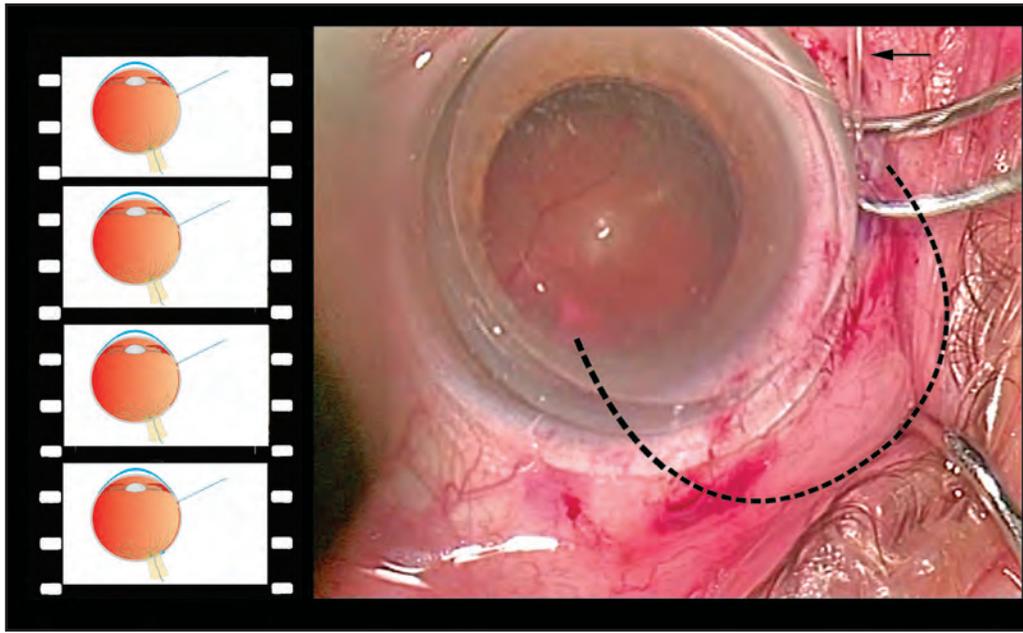


Figure 5: The ophthalmic microcatheter is inserted via an anterior scleral incision in the suprachoroidal space and moved to the area corresponding to the macula.

anterior scleral incision in the suprachoroidal space and moved to the area corresponding to the macula (Figure 5).

CONCLUSIONS

In the last decade PDT with verteporfin and the anti-VEGF pegaptanib and ranibizumab have significantly improved the prognosis of

exudative AMD. Nonetheless, visual acuity recovery is still partial and the treatment burden for patients and Health Care Systems has significantly increased.

New pharmacogenetic evidences show that genetic variants might significantly affect the response to treatments. Two retrospective analyses from the same group reported that patients with the CFH CC genotype responded

to treatment with intravitreal bevacizumab and verteporfin PDT significantly worse than did those with the CFH TC and TT genotypes while no association in treatment response was related to LOC387715 A69S variant.^{104,105}

New drugs are in clinical trials: VEGF Trap is a receptor decoy that targets VEGF with higher affinity than other available anti-VEGF agents.¹⁰⁶ Other promising therapeutic strategies are focused on ameliorating delivery of drugs and on new molecules designed to inhibit VEGF production by silencing RNAs (SiRNA) or block VEGF post-receptorial cascade via tyrosine kinase inhibitors. Moreover inhibitors of other proangiogenic molecules involved in the neovascular process (particularly interesting is E10030, an anti platelet derived growth factor studied in combination with anti-VEGF) are under development.¹⁰⁶⁻¹¹⁰

Future AMD strategies will be chosen upon single patient conditions on the base of a better knowledge of genetic and environmental risk factors and with multi-approach surgical and medical treatment options.¹⁰²

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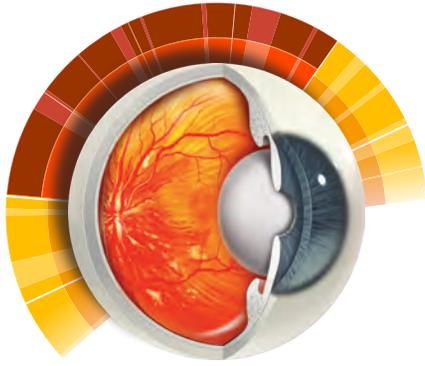


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20

Central Serous Chorioretinopathy

PRAN N. NAGPAL, MD.,
DHIREN BUJARBORUA, MD.,
ANIL PATIL, MD.

Introduction

Central serous chorioretinopathy (CSC / CSCR) most popularly known as “CSR (Central Serous Retinopathy)” is a sporadic disease of unknown etiology, characterized by blister like serous detachment of neurosensory retina and retinal pigment epithelium (RPE) in the posterior pole of the eye, usually involving the macula with angiographically demonstrable choroidal hyperpermeability and RPE leakage. This condition was first described by von Graefe¹ in 1866 as “Relapsing Central Luetic Retinitis”.

Demography

The reported incidence of this disease in general population is one case a year in every 22,000 inhabitants² and it accounts for about 5% of the cases attending the retina specialist³. It is now considered to be one of the ten most common diseases of the posterior segment of the eye⁴. It typically affects males

between 20 to 50 years of age. One recent study revealed mean annual age-adjusted incidences per 1,000,000 were 9.9 per men and 1.7 per women⁵. Patients diagnosed at 50 years or older are found to have bilateral disease, demonstrate a decreased male predominance (2.6:1), and show more diffuse RPE changes. Furthermore, these patients are more likely to have systemic hypertension or a history of corticosteroid use⁶. It is usually a self-limited disease, as the sensory detachment resolves spontaneously with fairly good recovery of vision, but in patients with recurrent episodes and chronic clinical course, significant visual loss can occur along with widespread RPE damage and retinal dysfunction.

Predisposing Conditions

Psychological stress associated with sympathetic arousal has long been considered to be an important risk factor for development of CSC. As stress theory empathizes, negative stress (or distress) derives from a negative relationship between environment



(e.g. critical life events) and personality. A recent study⁷ observed personality based difficulties in emotional regulation associated with hostility in CSC cases. Association of type A personality with this ailment is now well established⁸. These types of people are also prone to hypertension and coronary heart disease.

CSC appears to be more common among Caucasians, Hispanics and Orientals⁹, but it is thought to be uncommon among African Americans¹⁰. A variant of CSC which is characterized by bullous exudative detachment is mostly seen in Asian countries, particularly in north-eastern part of it. CSC develops mostly in hyperopic eyes.

Cigarette smoking, uncontrolled systemic hypertension, pregnancy, allergic respiratory disease,¹¹ use of Sildenafil citrate,¹² systemic corticosteroid therapy,¹³ endogenous mineralo corticosteroid dysfunction,¹⁴ psoriasis,¹⁵ systemic lupus erythematosus,¹⁶ obstructive sleep apnea syndrome (OSAS)¹⁷ – appear to be probable risk factors.

A recent report¹⁸ from Europe suggests that Helicobacter Pylori mediated immune mechanism might be encountered in the pathophysiology of CSC.

Pathophysiology of CSC

The basic pathology of CSC is now considered to be an idiopathic choroidal vascular hyperpermeability¹⁹ and this excess permeability appears to be due to adrenergic alteration of the macular retina⁸. The RPE barrier damage is basically secondary to excessive work load of the ionic pumps, but could

also be primary as there are experimental evidences^{20, 21} of presence of adrenergic receptors in RPE. Several Indocyanine Green Angiography (ICGA) studies²²⁻²⁶ have shown presence of multiple hyperpermeable areas in the choroid, which were often bilateral though one eye was symptomatic. Several studies^{24,26} observed delayed filling of segments of choriocapillaries prior to the development of hyper-permeability. Kitaya et al²⁴ were of the opinion that small, localized ischemic regions caused by non-perfusion or vasoconstriction of the choriocapillaries may induce collateral choriocapillary congestion around this region. However; a decrease in venous outflow of these areas may also have the effect of delaying the observed dye filling. The presence of fibrin in the detached space itself indicates that there is sufficient alteration in the permeability of the choriocapillaries and the RPE¹⁹. As the choriocapillaries are fenestrated, the interstitial fluid within the choroid can be expected to have a large range of molecules. Normally resorption of fluid and protein molecules within the choroid primarily occurs by free exchange through these fenestrated vessels and some excess amount is also drained through the sclera¹⁹. In acute CSC, the amount of fluid and solutes are definitely more than what the RPE cells normally can cope with. Vascular endothelial growth factor (VEGF) is produced by damaged retinal and choroidal cells when abnormal perfusion causes ischemia. By uncoupling endothelial cell-to cell junctions, VEGF causes vascular permeability and edema²⁷. The affected RPE cells start leaking fluid that would move towards the retina as there is less resistance in this direction. Several investigators^{22, 28-33} observed that the increase in interstitial hydrostatic pressure in the choroid drives the fluid towards the retina and leads to the development of PED



and microrips at the junction of attached and detached RPE or along the decompensated RPE cells that cause fluid leak into the subretinal space. The micro rents usually occur in the parafoveal region. Kitaya et al²⁴ observed foveal choroidal blood flow in eyes with CSC to be 45% less than the fellow normal eyes. Several Optical Coherence Tomography (OCT) studies³⁴⁻³⁶ noticed thickening of retinal layers in acute CSC. This finding indicates that enough of serous fluid enters the retinal stroma in the acute phase of the disease and retinal separation usually occurs in the posterior pole where the leaks develop. Once the detachment occurs, it would continue to enlarge until sufficient normal RPE is exposed to the exuded fluid which would drain it out at a rate equal to the inflow rate through the leak.²⁸ Thus, the detached space in CSC has a dynamic environment into which, and from which, there is a continuous flux of water, ions, and protein.³⁷

Role of Glucocorticoids

Corticosteroids were once used for the treatment of CSC, but now it has turned out to be a precipitating factor for the development of CSC.^{8,38-40} In the published reports, almost all the routes of administration of corticosteroid have been implicated for the development or exacerbation of this disease. Garg et al⁴¹ found statistically significant higher incidence of endogenous cortisol level in urine and plasma of patients suffering from CSC.

Corticosteroids and the catecholamines can produce CSC by following mechanisms: Corticosteroids may cause increased capillary fragility and hyperpermeability; Affect the

production of nitric oxide, prostaglandins, and free radicals, which may affect the regulation of blood flow in the choroids; Inhibit formation of collagen, which is the main component of Bruch's membrane; Alter ion water transport of epithelia; May directly damage the RPE cells or their tight junctions; May delay any reparative process in damaged RPE cells, by suppressing the synthesis of extracellular matrix components and inhibiting fibroblastic activity; Can influence the transcription and expression of adrenergic receptor genes and regulate adrenergic receptors. Stimulation of adrenergic receptors within the choroidal circulation results in release of secondary messengers (e.g. cAMP) and this may produce the vascular or RPE changes that result in CSC; Increase catecholamine mediated vasoconstriction; Epinephrine could induce apoptosis in a dose- and time-dependent manner in animal RPE cells. Such studies in human RPE cells are still lacking.⁴²

Clinical Presentation

Symptoms

The most frequent complaints are: blurred vision, positive scotoma, micropsia and metamorphopsia. The fall of vision is usually mild, but may be alarming. There may be mild aching pain in the eye, impaired colour vision; blurred near vision; impaired night vision; spontaneous entoptics; light flashes; photophobia and impaired depth perception. Sometimes migraine-like headache may precede or accompany the onset. Sometimes patient develops chromatopsia and in such a situation patient feels that they are seeing

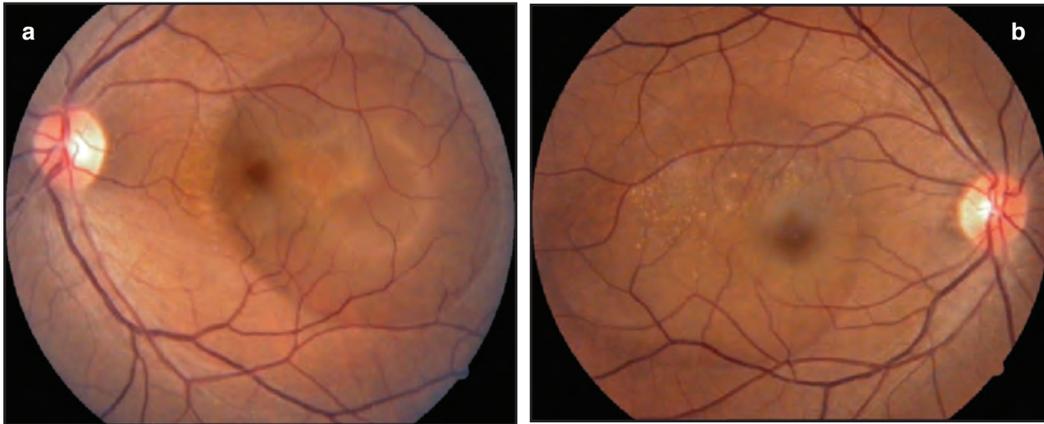
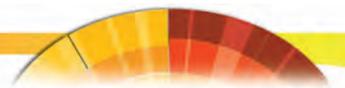


Figure 1 a-b: a) Fundus photograph of CSC with fibrin deposit. b) Fundus photograph of CSC with subretinal precipitates.

the objects through yellow or brown glass. Rarely patients also complain of cyanopsia.

Signs

CSC usually develops in the posterior pole of the eye as round or ovoid blister-like sensory retinal detachment of various sizes. The subretinal serous fluid is usually clear, but patchy turbidity may be seen due to presence of fibrin (Figure 1a). After few weeks of onset of the disease, tiny irregular white or yellow flecks become deposited on the posterior surface of the retina (Figure 1b). A recent OCT study⁴³ suggests that early granular deposits may be composed of fragments of photoreceptor outer segments that accumulate when the phagocytosis photoreceptor outer segment material is disrupted by the serous detachment of the retina.

Retinal Pigment Epithelial Detachment (PED)

Isolated PEDs may be seen in addition to sensory retinal detachment. PEDs may vary in size, but they are usually less than 0.25 disc diameter. At times PED lying under CSC is difficult to appreciate and it needs fluorescein angiography or OCT for detection. Giovannini et al⁴⁴ observed choroidal hyperpermeability in 83.3% and irregular choroidal venous dilation in 33.3% of cases at the site or within an area of one disc diameter size from the PED. The Idiopathic PEDs are a variant of CSC. Spitznas⁴⁵ categorized these as Type II CSC.

Subretinal Fibrin Deposit in CSC

In the initial phase, the subretinal fibrin produces a pale hazy appearance of the



subretinal fluid. This turbid fluid probably contains too little fibrin. Presumably with higher concentration of fibrin, the subretinal fluid becomes frankly opaque. Eventually, the fibrin plaque undergoes fibrinolysis and in majority it disappears. But fibrin can stimulate the RPE to undergo fibrocytic proliferation and to develop into fibrocyte-like cells. These cells ultimately form a membrane and it acts as a scaffold for secondary cellular proliferation.⁴⁶ Unusual sequelae of the subretinal fibrin deposit could be RPE rip, vascularization of the scar, and tenting up of the retina in the macula.

Subretinal Lipid Deposits

Occasionally subretinal lipid deposits may be seen in older patients with chronic CSC. They appear as discrete, hard-edged, subretinal accumulations usually at the border of the detachment, sometimes over the detachment and occasionally along the course of the RPE atrophic tracts. Lipid deposits in chronic CSC are seen without any angiographic evidence of CNV.

Atypical Presentation of CSC

They are – Bullous or Severe variant of CSC; Cystoid macular edema; Ring retinal pigment epithelial window defect; Leopard spot pattern; Secondary choroidal vascularization; Retinal telangiectasia with lipid deposition; CSC simulating pattern dystrophy; CSC with retinitis pigmentosa; choroidal folds without any evidence of underlying scleritis and with episcleritis.

CSC in Women

There is a significant difference in the male to female ratio in CSC cases. Cortisol responses to psychologic stress was found to be more in male than in female.⁴⁷ CSC in otherwise healthy women tends to occur at an older age than men. The conditions commonly associated with CSC in women are—pregnancy and systemic lupus erythematosus. Elevation of catecholamine, corticosteroids, oestrogen and other hormone levels during pregnancy may be responsible for it. Increased levels of prostacyclin during the second and third trimester may be another important factor. Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation.

Natural History

CSC is a self-limited disease, but runs a very unpredictable course. However, the natural course of the disease seems to have 4 distinct patterns:^{48,49} (1) CSC with a single resolving episode; (2) Recurrent resolving CSC –recovery is complete before the recurrence; (3) Recurrent chronic CSC –recurrence before full recovery; and (4) Chronic CSC - following a single episode without any appreciable recovery. The symptoms / sensory retinal detachment (SRD) persist beyond the usual period of recovery, that is, 6 months. In majority (80 to 90%) spontaneous resolution occurs within 1 to 6 months and in 20% it lingers for more than this period.⁵⁰ But even after recovery, the quality of vision is not the same as before in all the cases. The improvement of vision may continue for more than 1 year following resolution.



Figure 2: FFA Montage picture showing RPE track in chronic CSC.

Recurrence occurs in about 30 to 50% of all cases and 10% have three or more episodes. Almost 50% of the patients have a recurrence within 1 year of the primary episode. Wang et al⁵¹ observed foveal attenuation in cases of 4 months or more duration. Poor visual outcome may also be due to development of cystic degeneration of the macula or cystoid macular edema or due to development of a macular choroidal neovascular membrane.

Chronic CSC

Some investigators consider Diffuse Retinal Pigment Epitheliopathy (DRPE) to be synonymous with chronic CSC. In 1977 Zweng and Little⁵² coined this term for a condition, which had diffuse hyper- and hypo-pigmentation in the RPE, shallow sensory retinal detachment (SRD), no active fluorescein leak, a chronic

course, often bilateral, recurrent in nature, poor visual prognosis, and the patients were on an average 3.4 years older than those with CSC (Figure 2). Such cases had been documented earlier also, but no name was assigned to it. Initially some investigators thought it to be a separate condition from the CSC. Yannuzzi et al⁵³ described these cases under the heading of "Central Serous Pigment Epitheliopathy" (CSPE). Jalkh et al⁵⁴ reported their series under the synonym of "Retinal Pigment Epithelial Decompensation" (RPED). Subsequently many investigators considered it to be a more severe and rarer form of CSC occurring in patients older than 50 years, particularly in Asian and Hispanic patients. Castro-Correia et al⁴⁸ thought it to be the terminal stage of the exudative bullous type of CSC. But a recent study⁵⁵ had shown that it is the prolonged persistence of chronic SRD, which may be following a single acute episode or in recurrent cases with prolonged recovery time in each episode is required for its development. It is not necessary that the detachment will have to be massive and bullous. This study analyzing the data by logistic regression technique found that persistence of SRD at least for about 1.5 years was needed for development of RPE atrophy. This study also observed that DRPE passes through two stages: (1) Stage of RPE decompensation, which is probably reversible up to a certain period of time. (2) Stage of RPE atrophy. Clinically this stage appears to be a burnt out stage, but FA often reveals few decompensatory leaks and rarely subretinal hemorrhage may occur. It has also been observed⁵⁵ that not only DRPE cases are detected in the older age group, they are also found to be more common in patients developing their first acute



episode at a later age. DRPE is found to be more common in chronic cases. Moreover, presence of fairly big leaking PED contributes for the development of DRPE. As each and every case of chronic CSC does not develop extensive RPE degeneration, DRPE should be considered as a variant of it.

Bilaterality of CSC

CSC was once considered as a unilateral disease, but now the literature documents 5-35% incidence of bilateral CSC. It has also been documented that this tendency increases with age. According to Gass⁴⁰, approximately 10 to 25% develop symptomatic detachment in the opposite eye. Bujarborua et al⁵⁶ found the overall prevalence of bilateral pathology of CSC to be 44.54% at the initial visit using FA as the only investigative procedure. Yannuzzi et al (1979)⁵⁷ reported that 10% of the patients of their series had a concomitant acute SRD in the fellow eye and additional 12% developed the same during the follow-up period ranging from 2 to 8 years. They also observed RPE atrophy and pigmentary changes in about 80% of the fellow eyes by the end of their period of observation. Spaide et al⁵⁸ observed choroidal vascular permeability in both eyes of 96.90% of patients aged 50 years and older, even if the patients had unilateral visual disturbance. Another study²³ observed persistence of the choroidal vascular abnormality in the symptomatic eyes after cessation of leakage during the follow-up period that ranged from 6 – 48 months. The majority of the fellow asymptomatic eyes also had similar findings. Shiraki et al⁵⁹ made

similar observation in severe variant of CSC. Guyer⁶⁹ detected many occult small PEDs in the fellow eyes, which were not observed clinically and by FA. Other investigative procedures like multifocal electroretinography^{61,62}, contrast sensitivity⁶³ and assessment of colour vision⁶⁴ also detected significant changes in the asymptomatic fellow eyes.

Investigative Procedures in CSC

Fluorescein Angiographic Features

Fluorescein angiography in CSC reveals various types of leaks at the level of RPE depending on the stage of the disease. These leaks are seen in about 95% of all cases of all types of CSC.⁶⁵

Smokestack leak: It is considered to be the classic CSC leak (Figure 3a-c). In general, sensory retinal detachments (SRD) having this type of leak is larger than those with other types of focal leak.²⁸ Rarely the dye spreads inferiorly or horizontally.⁶⁶ The reported prevalence of smokestack leak in literature varies from 7% to 29%. Shimizu and Tobari⁶⁷ believed that the osmotic pressure gradient between the two fluid systems leads to unidirectional fluid flow through the functional hole in the pigment epithelium. Marmor⁶⁸ believed that much of the spread of fluorescein seen angiographically may represent diffusion and convection rather than net fluid influx. A recent study³⁰ believed that besides these factors, a bigger micro RPE rip is needed for the development of

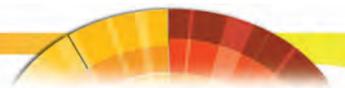


Figure 3 a-c: a) Fundus photograph. b and c) Depicting smoke stack leak on serial fluorescein angiogram.

smokestack leak. Occasionally unusual pattern of the ascending column of the dye is seen. Probably presence of fibrin alters the fluid dynamics of the subretinal space and produces the unusual pattern⁶⁹. One of the authors (DB) had the opportunity of observing more than one smokestack leaks inside the same detached cavity.

Ink-blot Leak: In majority of cases (60%), the point leak(s) that appear in the initial phase of the angiography slowly and symmetrically spread in all sides to about 1/4th disc diameter size (inkblot type). This type

of leak probably suggests late phase of the active disease process and the active stage itself may be of variable duration (Figures 4a-c and 5a-b).

Point Leaks: Some leaks do not expand much. These are the so called minimally expanding point leak⁷⁰, whose expansion is always less than 1/5th disc diameter in size. These types of leaks are usually found in subtle serous detachment of the retina.

Besides these - diffuse leak, decompensatory leak, window defects of various sizes and PEDs are visible on FA.

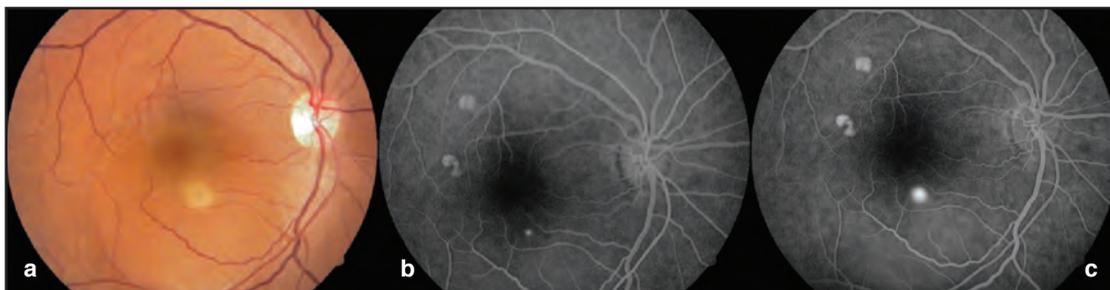


Figure 4 a-c: a) Fundus photograph. b and c) Depicting ink-blot leak below the foveal avascular zone.

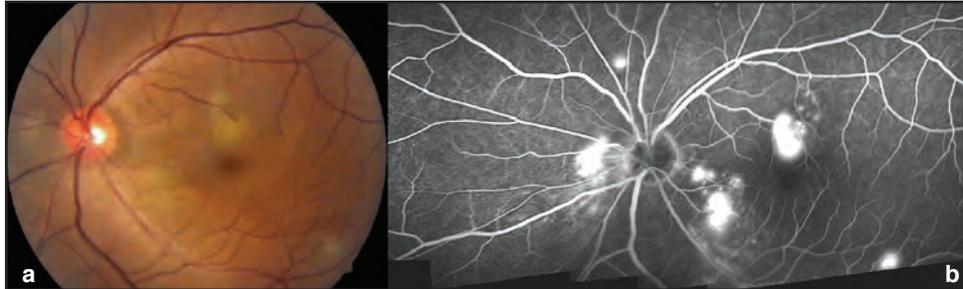


Figure 5 a-b: a) Fundus picture. b) Montage Fluorescein angiogram showing ink-blot leaks and PEDs.

After spontaneous resolution of CSC, the healed scar with persistent leakage may be there for sometime. Whereas, in some cases there is no angiographic finding. PEDs persist till it collapses spontaneously. In case of recurrence of the acute episode, in about 80% of cases, the new point of leakage is located within 1 mm of the previous leak.

Indocyanine Green Angiographic Features

Several investigators^{22-26,71} have shown presence of multiple hyperpermeable areas in the choroid (Figure 6a-b), which were often bilateral though one eye was symptomatic. Several studies^{25, 26, 71} have found the FA

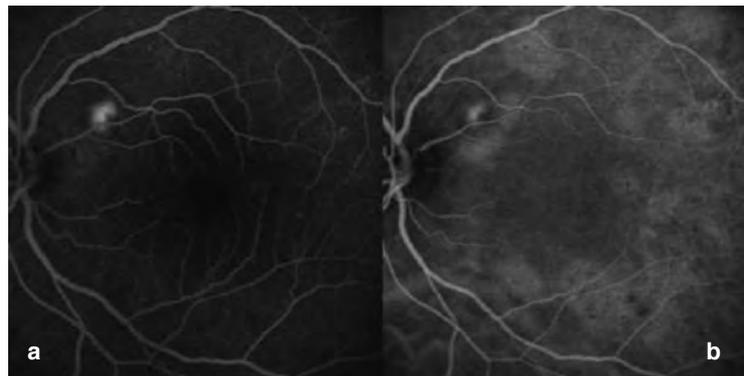


Figure 6 a-b: a) Depicting FA findings and b) Depicting the ICGA findings of the same fundus showing multiple hyperpermeable areas.

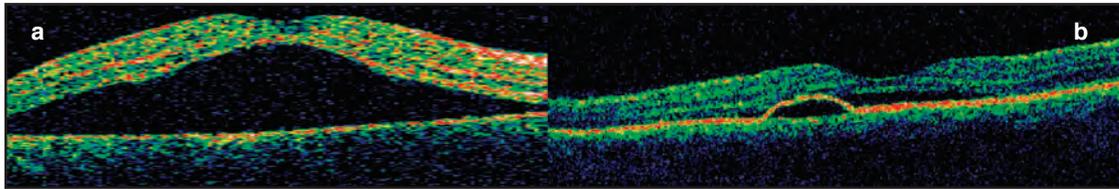
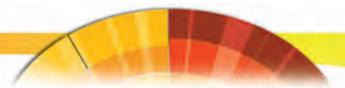


Figure 7 a-b: OCT showing a) subsensory fluid accumulation in CSC; b) detected shallow SRD along with PED.

leaks at the level of RPE to be contiguous with the areas of choroidal hyperpermeability, but some such areas were also seen without associated leak.^{22, 24, 71, 72} However, such areas develop leak in the follow-up period⁷¹ Several investigators^{23, 25} noted choroidal venous dilatation. The smokestack phenomenon is very unusual in ICGA.^{26,66} A recent OCT study⁷³ found PED (91%) and RPE bulge (89%) in the areas of choroidal vascular hyperpermeability. Even in quiescent CSC, areas of vascular hyper-permeability remain visible during ICG video angiography. A study from Japan⁷⁴ in which 9 eyes with history of CSC were followed up by ICGA for more than 5 years showed choroidal hyperfluorescence in all the eyes and associated choroidal venous dilatation in 6 eyes. Three of these eyes had recurrence during the follow up period.

Optical Coherence Tomography (OCT)

OCT can detect detachments that remained undetected in FA. It can also detect subretinal deposits like fibrin and subretinal precipitates (Figures 7a-b and 8). Iida and co-workers (2000)⁷⁵ utilizing OCT 2000 (Carl Zeiss Meditec) found the detached sensory retina to be thickened in acute stage of the disease. Piccolino and co-workers (2005)⁷⁶ using the Stratus OCT (Carl Zeiss Meditec) could detect changes indicative of even, granulated, and atrophic profiles in the foveal structure in the photoreceptor layer of some detached retina. Some investigators^{30,77} observed cystoid macular degeneration and foveal atrophy after resolution of the sensory retinal detachment

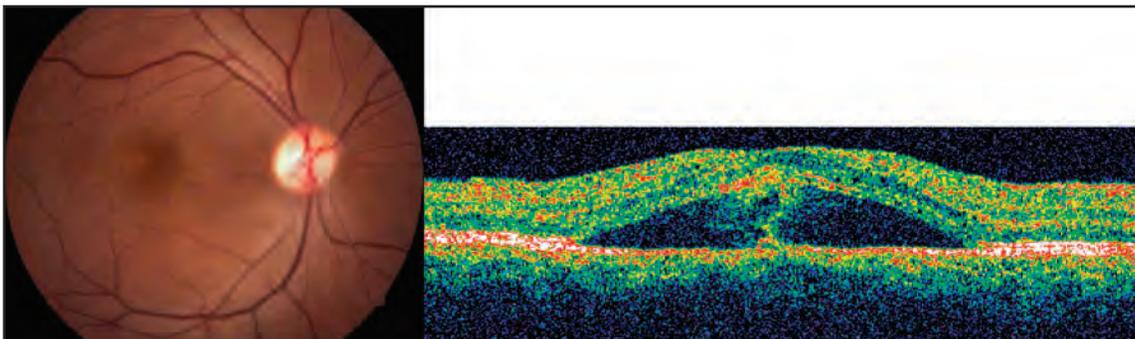


Figure 8: Fundus picture and OCT image showing subretinal fibrin deposit.



in eyes having visual loss. They used OCT 2000. Recently introduced Ultra-high resolution OCT provides an axial resolution of approximately 3 μm that allows improved visualization of the external limiting membrane (ELM), photoreceptor inner and outer segment junctions (IS / OS) and identification of pathologic changes in the microstructure of the photoreceptor layer. Fourier-domain OCT (FD-OCT) provides a three dimensional view of these structures.

Fundus Autofluorescence (FAF) in CSC

This technique is designed to document the presence of lipofuscin in the RPE. Lipofuscin is a mixture of proteins, lipids, and small chromatophores generated as by-products of the retinoid cycle. The accumulation of lipofuscin in the RPE is due to impaired or overwhelmed lysosomal activity, leading to incompletely digested cellular debris^{78, 79}. The presence of FAF is thought to correspond to the accumulation or dispersion of lipofuscin in the subretinal space or RPE. Eandi et al,³⁰ observed hypoautofluorescence corresponding precisely to the site of the focal RPE leak seen on FA in acute CSC cases. Hyperautofluorescence is known to occur beneath a chronic detachment of the retina. This supports the concept that a mechanical defect or absence of RPE accounts for the leakage from the inner choroids to the subsensory space.

Multifocal electroretinography has been used to identify focal regions of decreased retinal function, even in asymptomatic or clinically inactive eyes⁶¹.

Microperimetry (using the Nidek MP-1 microperimeter) has also shown that, despite clinical resolution of CSC, there is lower retinal sensitivity in the macula even with 20/20 vision. Fixation studies showed stability of central fixation.

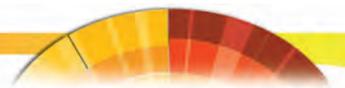
Differential Diagnosis

Following conditions may have to be differentiated from CSC: Age-related macular degeneration, Presumed ocular histoplasmosis syndrome, Idiopathic uveal effusion syndrome, Harada's disease, Posterior scleritis, Benign reactive lymphoid hyperplasia of the choroids, Toxoplasmosis, Sympathetic ophthalmia, Disseminated intravascular coagulative disease, Pathological myopia, Uveoscleritis, Choroidal tumours, Pit in optic nerve head, Idiopathic polypoidal choroidopathy, Severe hypertensive and renal diseases, Collagen-vascular diseases, Macular oedema, Irvine-Gass syndrome.

Management

Non-Drug Treatment

Reduce stress levels: Biofeedback, meditation, taking a philosophical approach to adversity, etc. Yoga may help; caffeine stimulates the pituitary gland and increases the cortisol level. Avoid caffeine containing drinks. Stop excess alcohol consumption. Try to avoid "cortisone treatments" as far as possible. Avoid unnecessary stress like disease, excessive exercise, crash diets, jet lag, pain, lack of sleep etc. Any form of infection increases cortisol levels. Monitor cortisol level if possible.



Medical Treatment

Many drugs had been tried for the treatment of CSC in the past, but without any convincing results. Still certain drugs like beta-blockers, acetazolamide (Diamox), certain anti-glucocorticoid agents and recently Bevacizumab (Avastin) are on use on investigational basis. Certain drug trails are going on to address the main causative factors as per present day's concept of the disease.

Beta-blockers like metoprolol, nadolol, and trimepranol have been used with controversial results. One recent double blind randomized controlled clinical trial from Iran⁸⁰ found that propranolol (20mg twice daily) cuts short the period of recovery and thereby eliminates the need for laser therapy. But it does not have any effect on visual recovery and its effect on recurrence rate could not be commented as it had a short term follow-up.

Acetazolamide (Diamox) was also shown to be effective as the propanalol⁸¹, but it can not prevent recurrences and final visual recovery did not differ much from the control group. Moreover, this drug is having considerable side affects.

Ketoconazole: This is an anti-fungal drug of Imidazole group. This is used as an adrenocorticoid antagonist in the treatment of Cushing's syndrome. A preliminary report from Manhattan Eye, Ear & Throat Hospital⁸² revealed that it lowers the endogenous cortisol level in CSC cases after 4 weeks treatment with 600 mg per day dose of the drug, but the median visual acuity, lesion height and the greatest linear dimension

remained unchanged during the month of treatment. It seems therapeutic effect would require longer time.

Bevacizumab (Avastin): Avastin, an antibody to VEGF (0.05 ml/1.25 mg intravitreal) is utilized in CSC cases to reduce the choroidal hyperpermeability and reverse the changes. Originally it was tried in chronic CSC cases. Now it has been tried in acute cases with encouraging result.⁴

Laser Photocoagulation in CSC

Since 1967 Laser has been introduced in the treatment of CSC. Light to moderate intensity applications of all modalities of laser like ruby, argon, krypton, diode and dye laser photocoagulation help in resolution of the detachment in CSC. Regarding the indications and time of intervention, the recommendations of Gass (1997)⁸³ can be summarized as follows:

- Wait for 4 months in case of primary episode.
- Wait for 6 months or more if the leak is less than 1/4th disc diameter away from the fovea.
- Wait for 1 month in patients with a history of several episodes of detachment in the same eye, if after each episode the patient has regained normal macular function.
- Prompt treatment is required (a) if the detachment is already present for 4 months or longer, (b) if patient has permanent



visual disturbance in either eye secondary to previous episodes of CSC, (c) for occupational reasons.

But regarding the time of intervention following points deserves attention before treating the cases.⁶⁶

- CSC either in the acute or in the chronic stage affects quality-of-life. Today's life is very stressful and highly competitive. No one can sit idle with visual problem hoping for an uncertain spontaneous recovery, unless and until they are compelled to because of non-availability of treatment.
- Many patients develop depression and extreme anxiety after acute onset of this disease. It is justifiable that by early treatment the patients should get rid of the annoying symptoms.
- Foveal attenuation occurs in CSC of more than 4 months duration and persistent BCVA reduction despite resolution of the detachment in such a situation.⁵¹ This study to be printed. They found no other likely cause of atrophy than the prolonged absence of contact between photoreceptors and retinal pigment epithelium. In this context, the reliability of the history of the patient regarding the duration of the symptoms deserves attention. In such a situation, early treatment is definitely justified.
- Sensory retinal detachment, which marginally spares the fovea, deserves immediate attention.

Long-Term Outcome of Laser Treatment in CSC

Annesley et al⁸⁴ in a long-term follow-up (10 years) of cases treated with photocoagulation observed that visual prognosis is extremely good in more than 85% of laser treated eyes, but 12% of the eyes in their study exhibited marked visual impairment.

Laser Treatment of Variant of CSC

Gass (1973)⁸⁵ reported promising anatomical results by argon laser photocoagulation in cases of "bullous retinal detachments associated with multiple serous detachments of the retinal pigment epithelium", which is a rare variant of CSC. Badrinath and Baig⁸⁶ did subretinal fluid drainage and photocoagulation in 5 eyes with severe variant of CSC. Though they could settle the retina, complications like incarceration of the retina in 2 eyes, retinal break and development of lenticular opacity in one eye each were observed. Chan et al⁸⁷ performed pars plana vitrectomy, perfluorocarbon liquid-assisted external drainage, and endolaser in a case of CSC with severe bullous serous retinal detachment. They had opted for this modality of treatment, as they could not apply laser to all the leaking spots. A report from Korea also showed successful result by doing vitrectomy and internal drainage of subretinal fluid in a case of bilateral severe variant of CSC.⁸⁸



Laser can treat DRPE cases and several investigators observed settlement of the chronic sensory detachment, slowing down of progression of visual loss and stabilization of vision at certain level. The laser is applied in a grid pattern. Krypton and argon laser have been used successfully for this purpose. How laser photocoagulation helps in resolution of the chronic detachment in DRPE is not yet fully understood. The probable explanations are—photocoagulation reduces leakage beneath the neurosensory retina by obliterating the choriocapillaries or photocoagulation may rejuvenate the RPE with reconstitution of the posterior blood-retinal barrier in areas of antecedent leakage.

Photodynamic Therapy (PDT) in CSC

Use of verteporfin and PDT was first reported in 2003 in the setting of CSC. Yannuzzi et al⁸⁹ used ICG angiography to first identify areas of choroidal hyperpermeability, which were subsequently treated by PDT. Several investigators have begun to use PDT as a first-line therapy for acute focal leaks from CSC with reported success. Most papers describe resolution of subretinal fluid within 1 month of treatment. The mechanism of action of PDT for treating CSC is postulated to be caused by short-term choriocapillaris hypoperfusion and long-term choroidal vascular remodeling. However, the application of conventional PDT in CSC can result in potential complications such as RPE atrophy, choroidal ischemia, and secondary choroidal neovascularization. To enhance the efficacy of PDT in treating CSC while minimizing

its side effects, the dose of verteporfin has been reduced and the time interval between infusion and laser application has also been reduced.⁹⁰ PDT has also been tried in cases of DRPE.⁹¹

ICG mediated photothrombosis is a technique using a low-intensity laser combined with ICG dye infusion to treat focal areas of hyperpermeability in the choroid. An 810-nm laser is applied after infusion of ICG dye. Without prior ICG dye, investigators have also used the 810-nm laser as transpupillary thermotherapy (TTT) with moderate success. But this method is risky. A recent report⁹² described severe retinal thermal injury in a 31-year-old man following this treatment modality.

Complications of Laser Treatment

1. Choroidal neovascularization at the site of photocoagulation. Small spot size and high power should be avoided.
2. Coagulation of macular venule or arteriole resulting in foveal ischemia and intra-retinal fibrosis. One must be very cautious in treating leaks near the margin of FAZ.
3. Creation of an appreciable positive paracentral scotoma or metamorphopsia secondary to excessive laser burn. Can be avoided by the use of minimal intensity coagulation, by avoiding treatment within FAZ and also by confining laser application to the area of incompetent pigment epithelium as demonstrated by angiography.



4. Slow but progressive enlargement of the area of RPE atrophy caused by the laser burn when the treatment site is close to the centre of the fovea.
5. Retinal distortion and accidental foveal burn.

Submacular Surgery in CSC

The current treatment options for the treatment of subfoveal or juxtafoveal choroidal neovascularization in CSC do not preserve macular function. Cooper et al⁹³ did submacular surgery for removal of choroidal neovascularization in 10 cases. They observed that the eyes, in which the central retinal RPE was preserved had the best visual outcome and the best cases for surgery appeared to be the eyes in which the neovascularization lied anterior to the RPE. Removal of such membranes could leave the underlying foveal pigment epithelium intact. As the choroidal neovascular membrane develops in CSC from a focal rather than diffuse abnormality of RPE, it offers the potential for preservation of central retinal pigment epithelium.

Conclusion

In the light of present day's concept of the pathophysiology of CSC, it should probably be defined as an idiopathic chronic disease of the choriocapillary-RPE complex of the eye, which is characterized by segmental hyperpermeability of the choroid and leak in RPE. The disease becomes symptomatic when sensory retinal detachment occurs dur-

ing acute exacerbation of the disease process due to various triggering factors.

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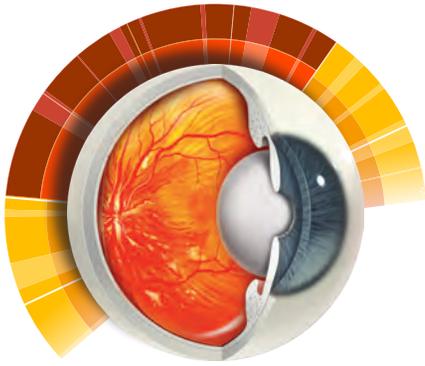
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Cystoid Macular Edema

FEDERICO GRAUE WIECHERS, MD.,
ENRIQUE ARIZA CAMACHO, MD

Description

Cystoid macular edema (CME) is a collection of fluid in both the outer plexiform and inner layers of the retina. It has a characteristic pattern of development of cystoid spaces in the foveal area due to perifoveal capillary bed changes. These changes disrupt the blood-retinal barrier, allowing fluid to enter, thus thickening the area.

Pathophysiology

Numerous ocular conditions predispose to cystoid macular edema. The exact cause for this pathology is unknown, but we know it occurs when the blood-ocular barrier is disrupted. Prostaglandins play an important role as mediators of intraocular inflammation, especially those of type E, which are strong mediators of the inflammatory response. Upon stimuli (surgical trauma), phospholipase A2 enzyme produces substances that originate

from fatty acids, such as the arachidonic acid, which is subsequently transformed into prostaglandin by the cyclooxygenase enzyme. When released in the aqueous humor, prostaglandins are responsible for an increase in permeability and vascular dilatation. The infiltration of inflammatory cells in the perifoveal capillary bed delivers other substances, such as bradykinin, and overflows to the extracellular spaces.⁽¹⁻⁴⁾ Some studies show that thickening and necrosis of Müller cells occur before development of cystoid spaces, which together with vascular changes, give rise to the characteristic petalloid pattern in fluorescein angiography.⁽⁵⁾ Other authors consider the fluid collection the result of the extracellular space expansion and do not refer to cellular changes.⁽⁶⁾ Development of edema in this area may be explained by the avascular anatomic characteristic of the fovea. Fluid re-absorption is highly limited in the extracellular space when a decompensation occurs; therefore, fluid tends to accumulate.⁽⁷⁾



The following factors have been postulated to cause the above mentioned changes in tissue:⁽⁷⁾

- Ultraviolet radiation exposure.
- Trauma of the ocular tissue.
- Ciliary body secondary irritation.
- Vitreous traction.
- Liberation of mediator elements due to diverse inflammatory changes.
- Induction by pharmaceutical drugs.

When cystoid macular edema does not resolve in 6 months and becomes chronic, it is associated with retinal thinning and photoreceptor changes as well as fibrosis, irreversible conditions which have an impact on the patients visual prognosis⁽¹⁾.

Types and Variations

Diverse ocular pathology may be associated with cystoid macular edema^(1,3,4):

- Inflammatory diseases (uveitis, specially pars planitis).
- Vascular diseases (branch or central vein occlusion and diabetic retinopathy).
- Degenerative diseases (premacular fibrosis).
- Dystrophies (retinitis pigmentosa).
- Surgical procedures (cataract surgery, retinal detachment surgery, penetrating keratoplasty, etc.).
- Use of pharmaceutical drugs (epinephrine, latanaprost, timolol).

In this chapter we will discuss cystoid macular edema caused by surgical procedures, specifically cataract extraction surgery.

CME associated with cataract extraction was first described by Irvine in 1953, and then by Gass and Norton in 1966. Initially, when cataract extraction was performed with intracapsular (ICCE) technique, 60% of cases developed cystoid macular edema. Later with newer techniques and equipment, specifically extracapsular cataract extraction (ECCE), the incidence of CME was reduced to 20%-30%, most of which will resolve within 6 months. Nowadays, with phacoemulsification, there is a reported incidence of CME of 1% to 2%. Only 1%-3% of patients eventually develop chronic cystoid macular with irreversible changes, which indicate a poor response to treatment and significant vision impairment.

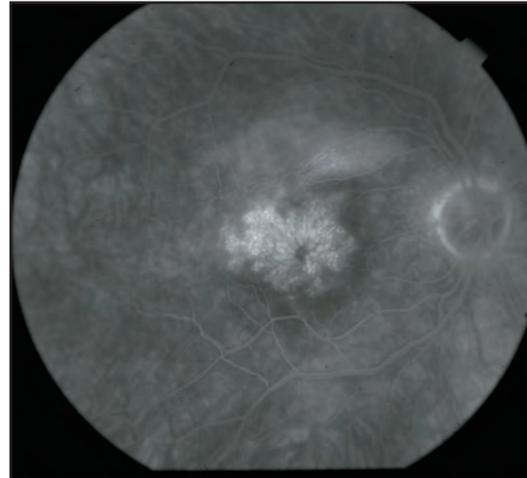
We can divide cystoid macular edema into two different types: acute and chronic. Acute CME usually occurs 6 weeks after surgery,^(8,9) and in most cases will resolve spontaneously, leaving no sequelae. Chronic CME persists longer than 6 months after surgery, and has a poorer prognosis.

It is also important to define two types of CME as they are frequently discussed in medical literature:

1. Angiographic cystoid macular edema refers to patients with no loss of visual acuity, but who show evidence of macular edema in a fluorescein angiogram with a classic petalloid pattern or Optical coherence tomography (OCT) (Figure 1).
2. Clinical cystoid macular edema is the usual term applied to patients with visual loss of 20/40 or worse, or 2 lines less than



Figure 1: Angiographic Cystoid Macular Edema. Characteristic fluorescein angiographic pattern of cystoid macular edema with accumulation of fluorescein dye in cystoid spaces and petaloid-shaped hyperfluorescence of the fovea. (Photo courtesy of Lawrence A. Yannuzzi, M.D., selected from his extensive retinal images collection with the collaboration of Kong-Chan Tang, M.D.)



expected of best corrected visual acuity in a given eye, as well as an angiographic changes. Acute clinical CME is the most prevalent type (1.87%).^(10,11)

Clinical Picture

Typically, a patient who has undergone cataract surgery approximately 6 weeks before presents only angiographic changes. If the patient has clinical CME, and/or visual loss of 20/40 or worse, it is important to obtain information about the surgical procedure (type of surgery, intraocular lens, history of CME in the other eye, postoperative hypotony and inflammation).⁽⁹⁾ Any complication during surgery such as disruption of the posterior capsule of the lens, retained lens matter, vitreous in the anterior segment, adhesion to iris or incarceration to the surgical wound, significant iris manipulation, or capsulotomy

with YAG laser postoperatively may cause an inflammatory condition of the eyeball that may lead to the onset of CME (Figure 2).

Subtle signs of an active inflammation such as mild flare, cells and ciliary injection may be detected. On biomicroscopic examination we have found conjunctival injection and disruption of the posterior capsule in 50% of patients. Other patients have some inflammatory type cells in the vitreous, and thickening at the perifoveal area, with intraretinal microcysts that occasionally collect a yellowish material inside, associated with an epiretinal membrane in 10% of cases. If the condition becomes chronic, cystoid coalescence may create a foveal cyst that subsequently develops a lamellar hole, or we may find retinal pigment epithelium changes in the area. Frequently, there may be signs of inflammation of the optic nerve^(7,12) (Figure 3).

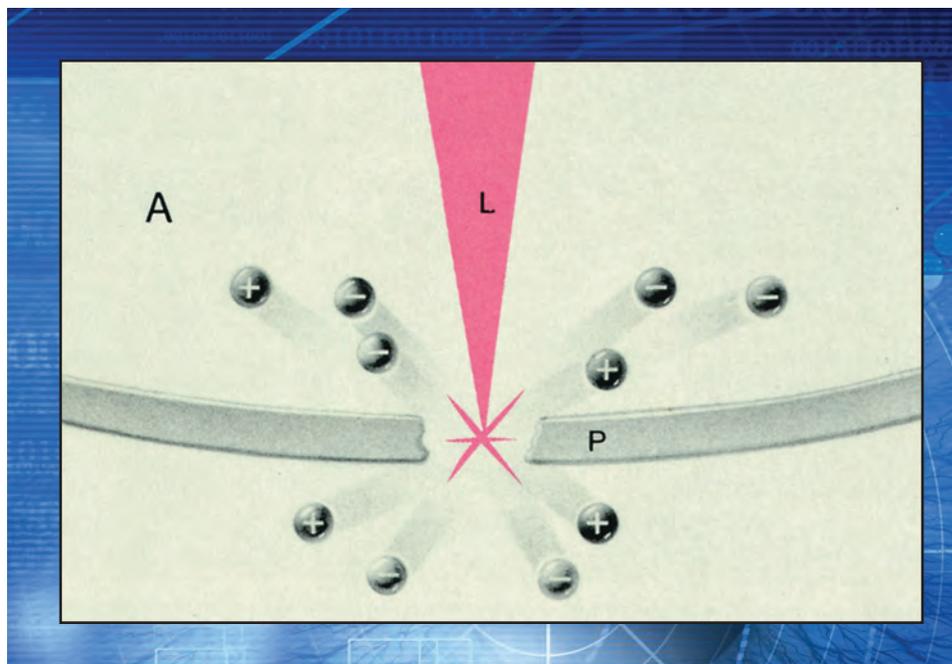


Figure 2: Principles of YAG Laser Surgery for Posterior Capsulotomy. The YAG laser (L) accomplishes tissue breakdown by ionization. Its clinical applications are related to its ability to cut and disrupt tissues within the ocular media. Here the posterior capsule (P) is being perforated by the laser (L) as the tissue is ionized (+ and -). The YAG laser does not need pigmented tissue for absorption as other forms of laser treatment do, which involve the process of photocoagulation. The latter requires pigment to be effective. There are reports that YAG laser posterior capsulotomy may lead to an increased incidence of CME if done within less than 6 months following cataract surgery. (Art from Jaypee-Highlights Medical Publications).

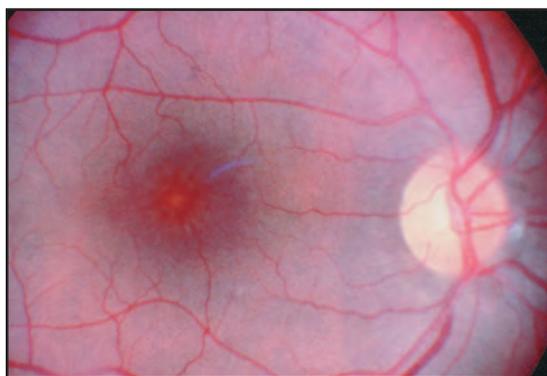


Figure 3: Clinical Cystoid Macular Edema. This photo shows the characteristic cystic changes in the macular region with accompanying fluid. Pseudophakic patient. (Photo courtesy of Lawrence A. Yannuzzi, M.D., selected from his extensive retinal images collection with the collaboration of Kong-Chan Tang, M.D.)

Diagnostic Support

Meticulous examination using a Goldmann contact lens on a patient with clear media is enough to diagnose clinical CME with an incidence of 1%-2%⁽¹¹⁾; however, if there is no evidence and visual loss cannot be explained, fluorescein angiography is recommended.

Angiographic CME has a reported incidence of 3% to 70%; 30% of patients following ECCE.^(9,11) Fluorescein angiography shows hyperfluorescence from different focuses during the early phases. This means that contrast material is leaking from perifoveal capillaries. The leakage increases in late phases, filling the cystoid spaces in the Henle fiber layer and manifesting the classic “petalloid” shape⁽¹²⁾ (Figure 4). The optic disk can also

be hyperfluorescent due to leakage from the nerve head capillaries because of inflammatory changes.

OCT provides noninvasive, noncontact, transpupillary cross-sectional detailed imaging of retinal structures with 8-10 μm axial resolution allowing quantification of macular thickness and mapping of retinal damage. OCT is useful to determine lesion depth as well as the alterations in the retinal anatomy showing that both the outer plexiform layer (OPL) and internal nuclear layer (INL) are preferred sites for retinal swelling or cystic spaces.⁽¹³⁾ This image technique helps in the diagnosis and follow-up for CME with or without treatment, especially in patients whom angiography is contraindicated for any medical reason (Figure 5).



Figure 4: Angiographic Cystoid Macular Edema. Fluorescein angiogram of CME. Please observe the characteristic petalloid pattern around the central fovea.

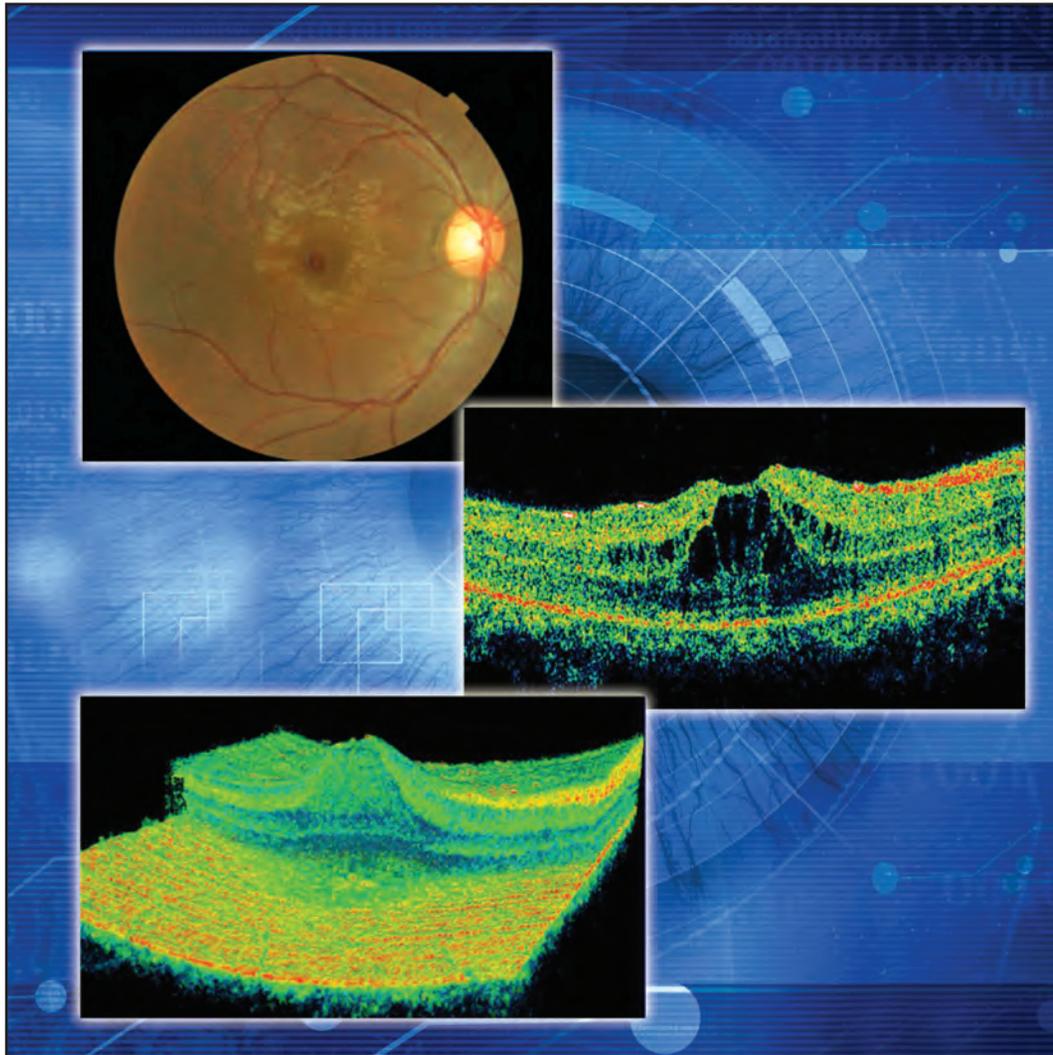


Figure 5: OCT Cystoid Macular Edema. Fundus image with cysts in the fovea. 6-mm horizontal scan: Distortion of the retina with cysts and subretinal fluid. OCT 3D image with elevation and distortion of the retina.



Other supportive test for these patients are used less often: fluorophotometry, which detects an increase in vascular permeability⁽¹²⁾; laser tomography, which supplies a three-dimensional quantitative analysis, allowing us to evaluate information regarding visual prognosis and macular cyst pathogenesis, together with fluorescein angiography.⁽¹⁴⁾

Medical Treatment

A large number of drugs have been investigated both for prophylaxis and treatment of an established CME. As we have already mentioned, the theory implicating prostaglandins as inductors of CME histopathologic changes was a guideline for using certain drugs which act on prostaglandin synthesis, helping to accomplish an average lower CME incidence from 10.1% in the control group to 4.9% the group receiving prophylactic treatment,⁽¹⁵⁾ as well as chronic CME resolution.

Indomethacin and ketorolac, non-steroidal antiinflammatory drugs (NSAIDs), belong to a group of useful drugs that act through non-selective inhibition of both isoforms of cyclooxygenase (COX-1, COX-2) who have distinct tissue expression patterns and transcriptional regulation mechanisms.^(16,17) COX is a catalytic enzyme that transforms arachidonic acid into prostaglandin. Oral indomethacin has been used in patients with CME, although a high daily dosage (100mg) is required to properly control the condition. Then undesirable side effects of the gastrointestinal tract and central nervous system changes may occur with subsequent cessation of treatment, especially

in elderly patients.⁽⁸⁾ Therefore, topical indomethacin has yielded better results.^(8,10)

Ketorolac, another non-steroidal anti-inflammatory drug, improved visual acuity by two or more lines in 67% of treated patients, with CME resolving within a shorter period of time, an average of 2.3 months. It is reported to improve contrast sensitivity in 55% of treated patients, and to cause disappearance of angiographic changes in 55% of patients who have had CME for more than 24 months. These improvements, however, would probably require long-term application of the drug.^(8,10) In combination with one steroid, ketorolac was shown to improve visual acuity by two or more lines in 89% of treated patients, within 2 months after initiation; with 89% contrast sensibility improvement and 77% improvement of angiographic changes, which proves its potential effect on CME.⁽¹⁶⁾

Expression of COX-2 is highly regulated and is markedly increased by inflammatory factors subsequent to tissue injury, producing rises in prostaglandins that are themselves mediators of inflammation.⁽¹⁷⁾ Valdecocix, celecoxib, rofecoxib are COX-2 inhibitors that allow effective treatment of inflammation while reducing side effects of NSAIDs. Increased cardiovascular risk and increased rate of skin reactions were observed when the application period lasted at least 12 months, reason why U.S. FDA removed it from the market as an chronic anti-inflammatory treatment. A prospective clinical trial showed that 10 mg of the COX-2 inhibitor valdecocix once daily for 3 weeks is effective and well tolerated in treating CME without any side effects.⁽¹⁸⁾



Nepafenac, a pro-drug of arylacetic acid NSAID introduced in 2005, has greater permeability that results in less active drug exposure to the cornea and greater drug concentration at the site of action. Due to its pro-drug property, a reservoir of parent drug that is later converted to amfenac may be created in the anterior chamber of the eye, prolonging the duration of the anti-inflammatory action. It has shown a reduction in visually significant CME in patients treated with nepafenac and prednisolone compared with patients treated with prednisolone alone (0% and 2%, respectively; P.0354).⁽¹⁹⁾

Acetazolamide may reduce CME as an inhibitor of carbonic anhydrase; the mechanism of action involves alteration of the polarity of the ionic transport systems in the retinal pigment epithelium cells, Müller cells, cone internal segments, and endothelial cells, where carbonic anhydrase is found. Encouraging results have been obtained with oral dosages of 500mg/12 or 24 hours.^(20,21)

Hyperbaric oxygen therapy is another option for treating CME, using highly concentrated oxygen to produce some changes in oxygenation and ocular blood flow. Even though favorable results have been obtained, these studies have included a follow-up period of no longer than 3 months.⁽⁷⁾

Corticosteroids inhibit synthesis of the enzyme phospholipase A2, thus both the cyclooxygenase and lipoxygenase pathways, lessening the production of substances such as arachidonic acid, which is a prostaglandin precursor and leukotrienes. These drugs thereby diminish the inflammatory process;⁽¹⁾

they also have anti-angiogenic, anti-edematous and anti-proliferative effects. Stern et al have used corticosteroids orally with a satisfactory response in 40 of 49 studied patients.⁽¹⁶⁾ Oral steroids, unfortunately, can cause a spectrum of systemic side effects, including osteoporosis, cushingoid state, adrenal suppression and exacerbation of diabetes.^(22,23) However, almost all steroids produce undesirable side effects, which subsequently cause some patients to abandon treatment.

Topical ocular steroids are associated with certain risks, such as glaucoma, posterior subcapsular cataracts, opportunistic infections, and delayed wound healing. Steroids have been injected into the sub-Tenon's space or have been used topically (prednisolone acetate)⁽¹⁰⁾ in an attempt to control the systemic side effects, with favorable results. After cessation of treatment, however, CME may recur. This can also happen with oral administration of corticosteroids. Increased intraocular pressure is a well-known possibility in patients with a significant response and a faster CME resolution. We do not yet have an explanation for this phenomenon.⁽²²⁾

Intravitreal use of corticosteroids has proved useful as a result of the anti-inflammatory effects and stabilization of the blood-retinal barrier (BRB). Intravitreal delivery allows the steroid to bypass the BRB, leading to a more concentrated dose of steroid for a prolonged period of time, although the duration of the action is typically short-term.^(22,23) The most common delivery is via direct injection through the pars plana, other methods include through a sustained-release or biodegradable implants, or injection of conjugate compounds.

Intraocular steroid sustained-delivery device that can help release a consistent amount of drug in a longer period of time are in development since most of the intravitreal drugs have a relative short intraocular half-life.⁽²³⁾ The DDS (Dexamethasone Posterior Segment Drug Delivery System, Allergan Inc.) is an implant of a biodegradable copolymer of lactic acid and glycolic acid that provides gradual release of 350 or 700 μg of dexamethasone after inserted through a small pars plana incision or puncture (Figure 6).

The intraocular half-life of dexamethasone has increased from approximately 3 hours up to 6 months after insertion. The polymer slowly biodegrades until it dissolves completely.⁽²⁴⁾ Another implant containing 0.59 mg fluocinolone acetonide demonstrated efficacy in clinical trials. Eventually this technology can provide a better and longer intravitreal drug treatment without the hazard of multiple re-injections.

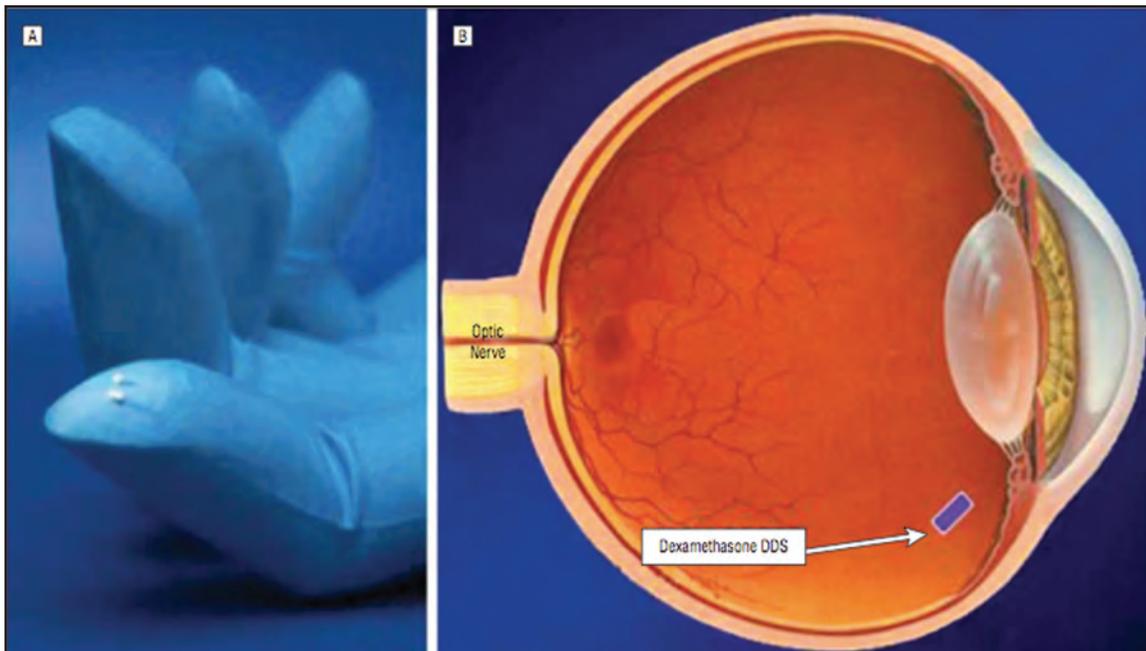


Figure 6: Dexamethasone Drug Delivery System (DDS) Implants.

Intravitreal injection of triamcinolone acetonide (TA) has proved long-term safety and efficacy. A 4-mg dose, in a non-vitreotomized eye, maintains measurable concentrations for approximately 3 months.⁽²³⁾ CME treated with 8-mg of intravitreal TA a month after injection

noted a decrease in macular thickness from a mean 502 to 233 μ m and a mean improvement in visual acuity of 3.7 Snellen lines; however the edema recurred in some cases two to 4 months after injection⁽²⁵⁾ (Figure 7).

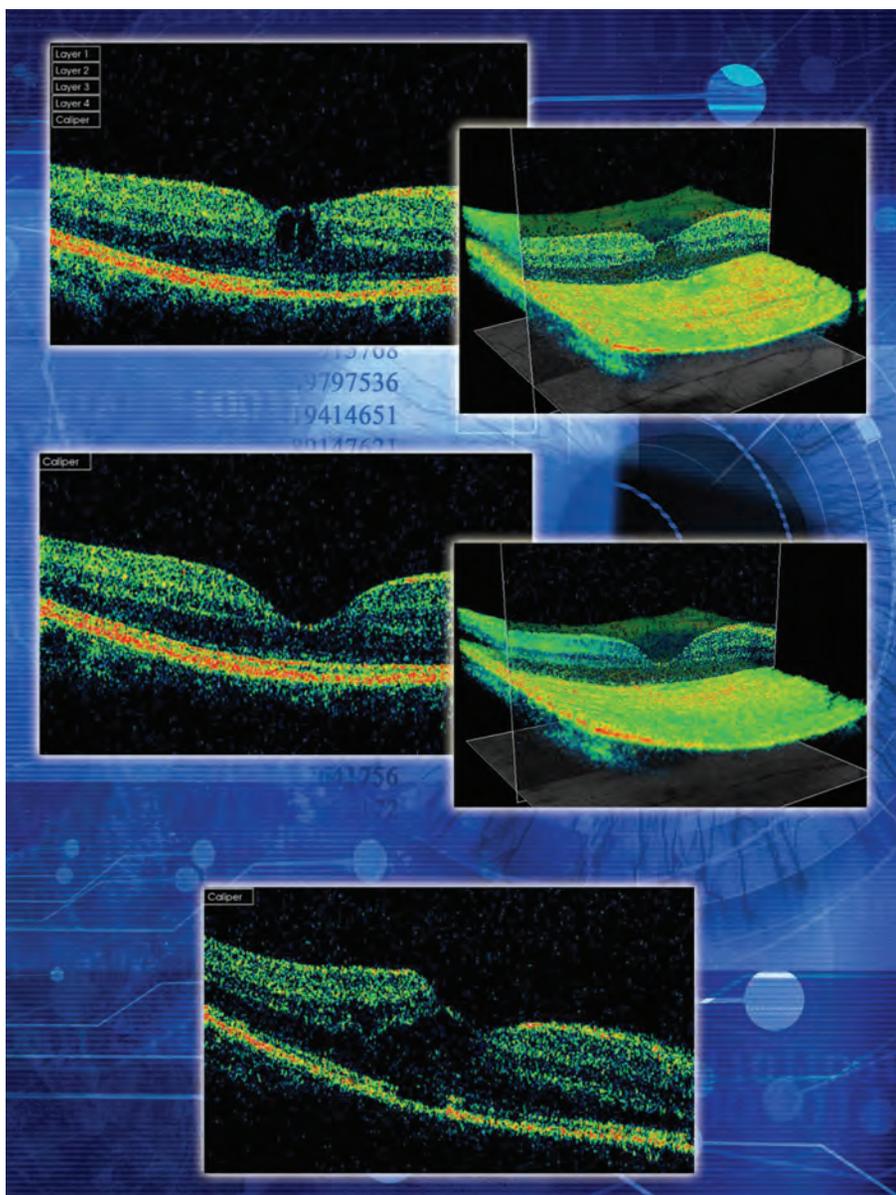


Figure 7: Intravitreal TA for CME. Horizontal OCT scan of CME after Intravitreal TA injection showing decrease in macular thickness and posterior recurrence of CME.



The main vehicle for TA is benzyl alcohol, which at higher concentrations, can damage the outer-segments and photoreceptors, reason why some support the idea to pour off the main vehicle. The possible complications after an intravitreal triamcinolone injection include endophthalmitis (0.5%), increased IOP (42%), retinal detachment, non-infectious endophthalmitis (1.6%), and cataract formation (24%).^(22,23,25)

Antiangiogenics (Bevacizumab, Ranibizumab), until recently, have been used off-label to treat a variety of ocular diseases as they inhibit the effects of vascular endothelial growth factor (VEGF) that has been implicated as a major angiogenic stimulus responsible for neovascularization and is also a potent permeability factor causing a breakdown of the BRB and increasing the permeability of the perifoveal capillary net with resultant fluid accumulation in the perifoveal retina.^(26,27) CME is related to the disruption of the BRB and blood-aqueous barrier and the inflammation induced by prostaglandins or other inflammatory mediators (cytokines, endotoxin and immune complex) resulting from an increased expression of VEGF.⁽²⁷⁾

Bevacizumab is a complete full-length humanized antibody that binds to all subtypes of VEGF. An open-label uncontrolled clinical study of 4303 injections in human eyes with 1.25 mg or 2.50 mg intravitreal bevacizumab, found systemic adverse events in 18 patients (1.5%) being the most frequent acute elevation of systemic blood pressure (7 cases 0.59%)

and ocular complications included 7 cases (0.16%) of bacterial endophthalmitis, 7 cases (0.16%) of tractional retinal detachment, 4 cases (0.09%) of uveitis, and a case (0.02%) each of rhegmatogenous retinal detachment and vitreous hemorrhage.⁽²⁸⁾

An interventional, retrospective multicenter study reviewed 25 consecutive patients (28 eyes) with pseudophakic CME treated with at least 1 intravitreal injection of 1.25 mg (16 eyes 57.1%) or 2.50 mg (12 eyes 42.9%) of Avastin 13 months (mean time) after surgery. A mean follow-up of 32 weeks revealed 28 eyes (71.4%) had improved best corrected visual acuity (BCVA) (≥ 2 ETDRS lines). The mean baseline BCVA was 20/160 (logMAR 0.92) and the mean final BCVA 20/63 (logMAR 0.50); the difference was statistically significant ($P < .0001$). The mean central macular thickness at baseline (466.3 μm ; range 208 to 784 μm) decreased significantly (264.5 μm ; range 176 to 513 μm) by the end of follow-up ($P < .0001$) (Figure 8 A-B). No statistically significant differences in duration, anatomical, or functional effectiveness between the 2 doses. Eight eyes (28.6%) required a second injection and 4 eyes (14.3%) a third injection on either group. No ocular or systemic effects were reported at 6 months.⁽²⁹⁾

This may be an excellent and safe treatment modality for patients with CME unresponsive to topical medications or patients who are steroid responders or hesitant to have corticosteroid treatment.

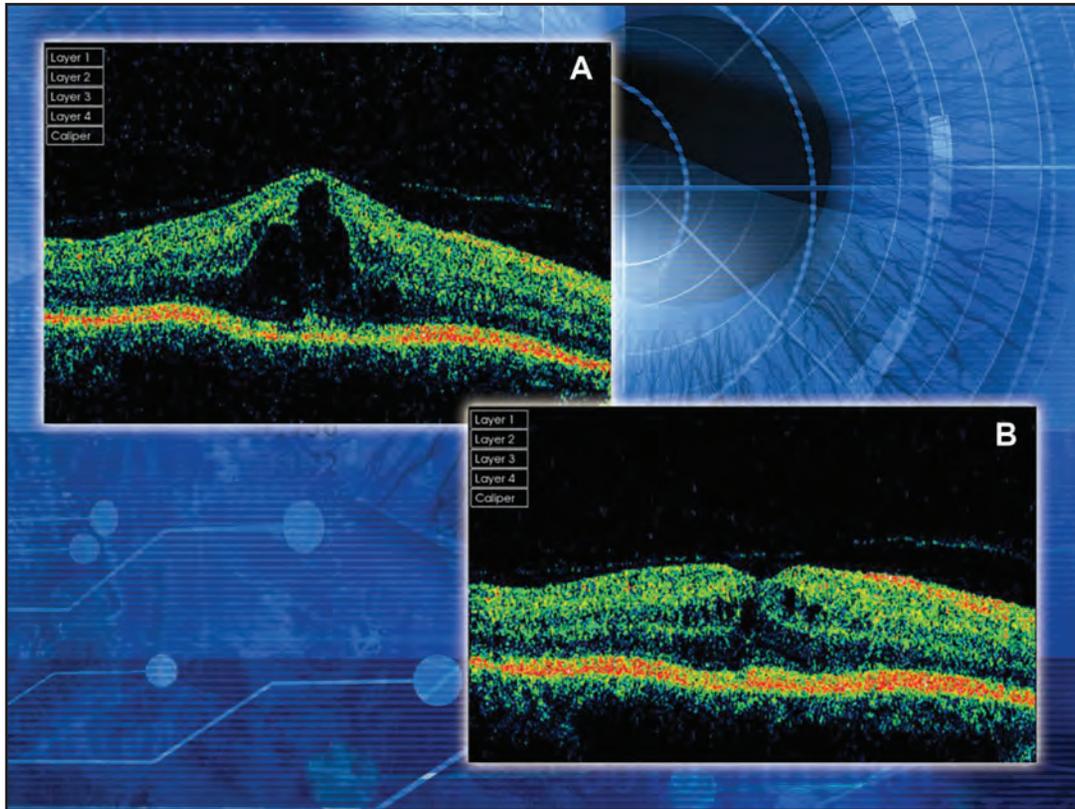


Figure 8 A-B: Intravitreal Bevacizumab for CME. **A)** Horizontal OCT scan showing CME with loss of normal foveal contour and thickening. **B)** Resolution of cystic spaces with restoration of foveal anatomy and thickness.

Surgical Treatment

Studies provide evidence to recommend vitrectomy as a therapeutic measure in patients with chronic CME presenting papillary distortion secondary to vitreous adherent to the corneo scleral wound in addition to anterior segment inflammatory signs (classic Irving-Gass syndrome) and with some posi-

tive response to medical therapy. Favorable results have been documented in aphakic and pseudophakic patients, with a postoperative improvement in visual acuity. The operation is recommended when visual acuity has remained stable for 2 or 3 months (since visual acuity fluctuation is well known in CME early phases), and also when visual acuity is 20/80 or worse within 2 years of the onset of the CME.^(30,31,32)



A significant finding in the above mentioned studies is that the majority of patients had posterior vitreous detachment. Only 3% of aphakic patients and no pseudophakic patients presented vitreous traction strands on the macula. Therefore, the mechanism of action in vitrectomy might involve removing a series of substances that are inflammatory mediators. This would reduce the CME but not lessen traction on the macular area, as one might suppose it would.⁽³⁰⁾

Recently with the advantage of high-resolution images obtained with OCT, new insights into the pathogenesis and progression of cystoid macular edema have been proposed. Similar to macular hole, tangential vitreomacular traction involving the internal limiting membrane (ILM) seems to play an important factor acting as a scaffold for proliferation of cellular components. ILM represents the structural boundary between the retina and the vitreous measuring an average of $2.5\mu\text{m}$ in thickness.^(33,34,35) Pars plana vitrectomy allows the complete removal of vitreous and posterior hyaloid as well as of any vitreous traction strands that can affect the macula, and by ILM peeling, it is possible to relieve any residual tangential traction and ensure complete removal of epiretinal tissues. Also ILM peeling can potentiate the effect of topically administered medications by removing a diffusion barrier.⁽³³⁾ ILM peeling can be achieved by using a blunt retinal pick, a bent MVR blade, a diamond dusted ILM scrapper or a vitreoretinal forceps; also staining of the ILM either with indocyanine green (ICG), trypan blue, TA and most recently brilliant blue G has made the removal easier

and safer, reducing the operating time and mechanical trauma to the retina.⁽³⁴⁾ Although the combined procedure is more challenging, with the possibility of severe complications like retinal tears, hemorrhages, RPE changes, macular phototoxicity and opening macular cysts, resulting in important damage to the fovea and a poor visual outcome.^(34,35)

Patients who present vitreous adherent to the surgical wound as a complication of cataract extraction may have anterior segment inflammatory changes, leading to the migration of substances towards the posterior pole and the onset of CME. YAG laser vitreolysis has been investigated as a treatment. It allows bisection of vitreous strands adherent to the cataract wound, thus resolving this pathology. Access is difficult, however, because of the location of the vitreous strands. Reports of this technique show its benefits, but the studies have several limitations: no control groups are mentioned, treatment has been given to patients with short-term CME evolution, and concurrent corticosteroid therapy was administered as well.

Conclusion

New techniques and better equipment have contributed to a dramatic decrease in the incidence of cystoid macular edema, especially secondary to cataract extraction surgery. However, CME still represents pathology that can cause a significant change in the visual prognosis of patients who presented no alterations before surgery. This is a surprisingly serious concern for the surgeon. The etiology



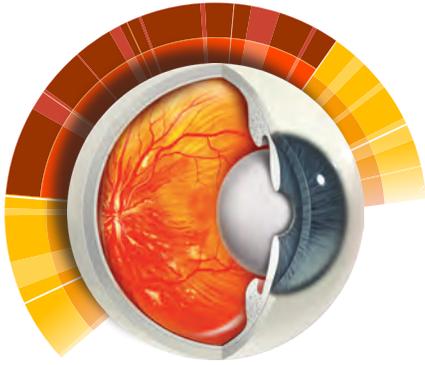
of this disease has not yet been totally elucidated; therefore, the types of treatment we know today are not completely effective. If properly prescribed and used, however, the available series of pharmaceutical drugs and available procedures will help reduce the irreversible damage caused by cystoid macular edema.

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Traction Maculopathies: Vitreomacular Traction Syndrome, Cellophane Maculopathy, Macular Pucker, Macular Hole

FERENC KUHN, MD, PH.D.,
ROBERT MORRIS, MD,
C. DOUGLAS WITHERSPOON, MD, FACS

Introduction

Traction can be defined as a synonym for force. On the macula, this force can manifest in two vectors: anteroposterior (i.e., originating in the vitreous body) or tangential (i.e., forming on the retinal surface; Figures 1A, 1B). (**Author's Note:** Traction force can also be created by subretinal scarring; this entity is not discussed here.) The resulting anatomical changes (retinal distortion, fold formation, vascular leakage etc.) can quickly lead to functional consequences in most cases; how early the patient seeks ophthalmologic consultation, though, shows great variability, due to the normal fellow eye's dominance as well as to the individual's personality and visual needs.

Vascular incompetence due to traction can occur as reflected in the abnormal fluorescein angiogram. Due to chronic traction-related

vascular incompetence, the macular tissue may become diffusely edematous. The fovea can develop cystic changes over time, which are usually reversible after traction release if the intervention is timely. In extreme cases, however, the untreated foveal cysts can develop into partial- or full-thickness holes. Long-standing traction can also produce separation (i.e., true detachment) of the neuroretina in an area involving the fovea or macula.

The cause of traction development is usually unknown (idiopathic); occasionally, the etiology is identifiable: trauma, inflammation, proliferative vitreoretinopathy, etc.

Classification

The term (coined by Robert Morris, MD) "traction maculopathy"¹ encompasses four distinct conditions and its common pathogenesis (see Table 1).

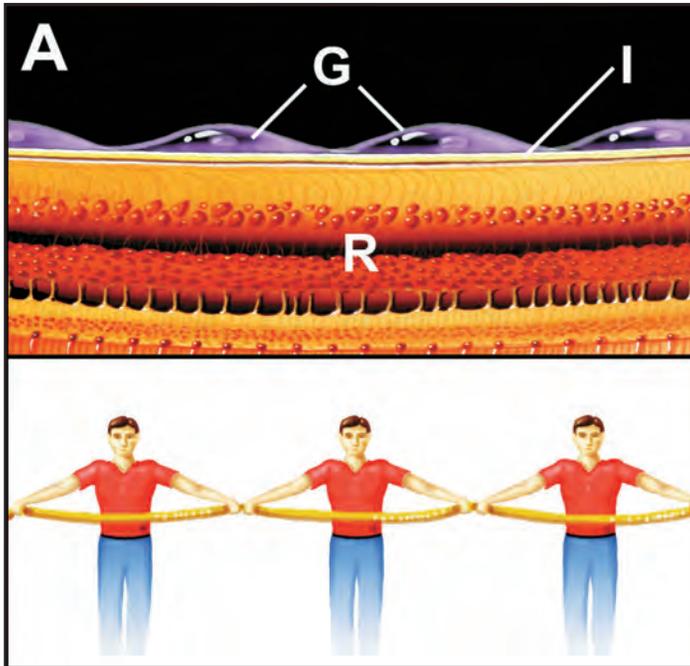


Figure 1A: Epimacular proliferation (EMP) before contraction (rope men). Glial cells (G), internal limiting membrane (I), retina (R). (Art from Jaypee - Highlights Medical Publishers).

Figure 1B: Epimacular proliferation (EMP) after contraction (rope men). Internal limiting membrane (I), retina (R). (Art from Jaypee - Highlights Medical Publishers).

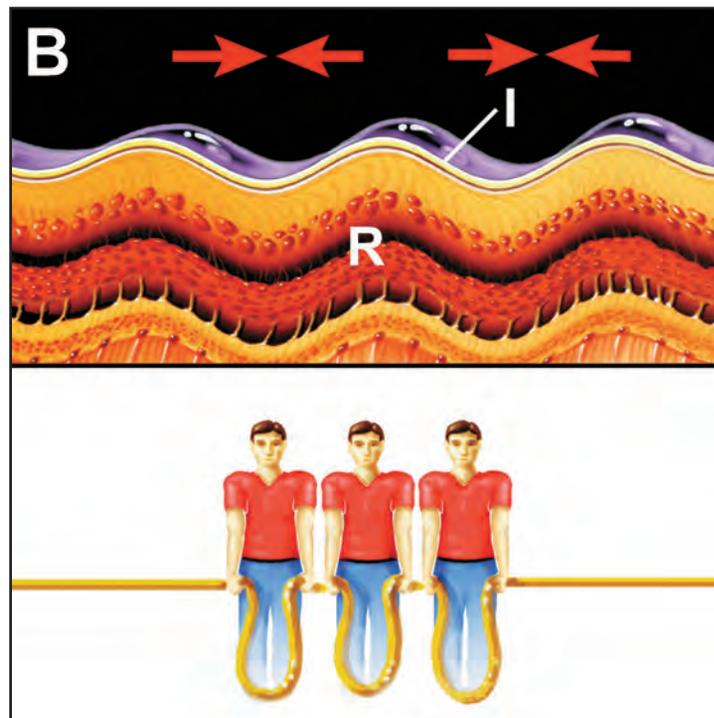


Table 1
The Classification of Traction Maculopathies

Name of Condition	Traction Force	Retinal Effect
Vitreomacular traction syndrome	Anteroposterior	Full-thickness
Cellophane maculopathy	Tangential	Surface
Epimacular proliferation (macular pucker)	Tangential	Partial-thickness (inner retina) to full-thickness
Macular hole	Anteroposterior and tangential	Full-thickness

Diagnosics

History. Although the condition may be a serendipitous finding, in most cases it is the patient who discovers the functional disturbance. A long history is important because it typically interferes with good visual recovery.

Visual function. A deterioration of **visual acuity** is the most common finding (and complaint given by the patient), but upon careful testing (and questioning), a distortion of vision is just as often found (hence the recommendation, in addition to the standard visual acuity testing, to utilize the **Amsler grid**, which shows deformation centrally). (**Author's Note:** The **Amsler grid** is a very effective initial diagnostic tool, but it is ineffective to detect further deterioration. The

human brain remembers the previously seen image and does not appreciate the subsequently shown image as new (false-negative test result). The reading speed is another valuable test: A significant drop in the speed of reading a standardized text (MNREAD) may be demonstrated. (**Author's Note:** This is a crucial advantage over the standard visual acuity testing: the latter measures the reading of single letters, as opposed to the closer-to-life situation of measuring reading ability with the MNREAD test).

Slit lamp biomicroscopy with a 90 D or, preferably, a contact lens. This is the most useful easily available diagnostic tool, allowing the ophthalmologist to view not only the macula in great detail (Figure 2) but also the certain vitreous pathologies (e.g., the presence anteroposterior traction if significant).



Figure 2: Fundusoscopic image of an epimacular proliferation. A distinct membrane in the macula as well as marked distortion of the blood vessels around the fovea can clearly be delineated. Fine retinal folding is also visible. (Image courtesy of Viktoria Mester, MD.)

Binocular ophthalmoscopy. Although giving fewer fine details than obtainable at the slit lamp, the binocular ophthalmoscope is of great value to show the entire vitreous cavity and widespread vitreoretinal pathologies. (**Author's Note:** i.e., seeing the “forest, not only the trees”). Foveal ectopia, which can cause diplopia, is easier to detect when one sees the entire posterior pole, not just a smaller central area of the retina, and compares this image with the fundus of the fellow eye.

Optical coherence tomography (OCT). This relatively new but rapidly evolving diagnostic modality is becoming the major weapon in the ophthalmologist's armamentarium to not only diagnose lesions that may be invisible otherwise (Figure 3A), but also to follow the macula over time as a noninvasive procedure (Figure 3B). The test is thus ever more commonly utilized for diagnosis as well as for following anatomical changes occurring spontaneously (natural history) or after surgery.

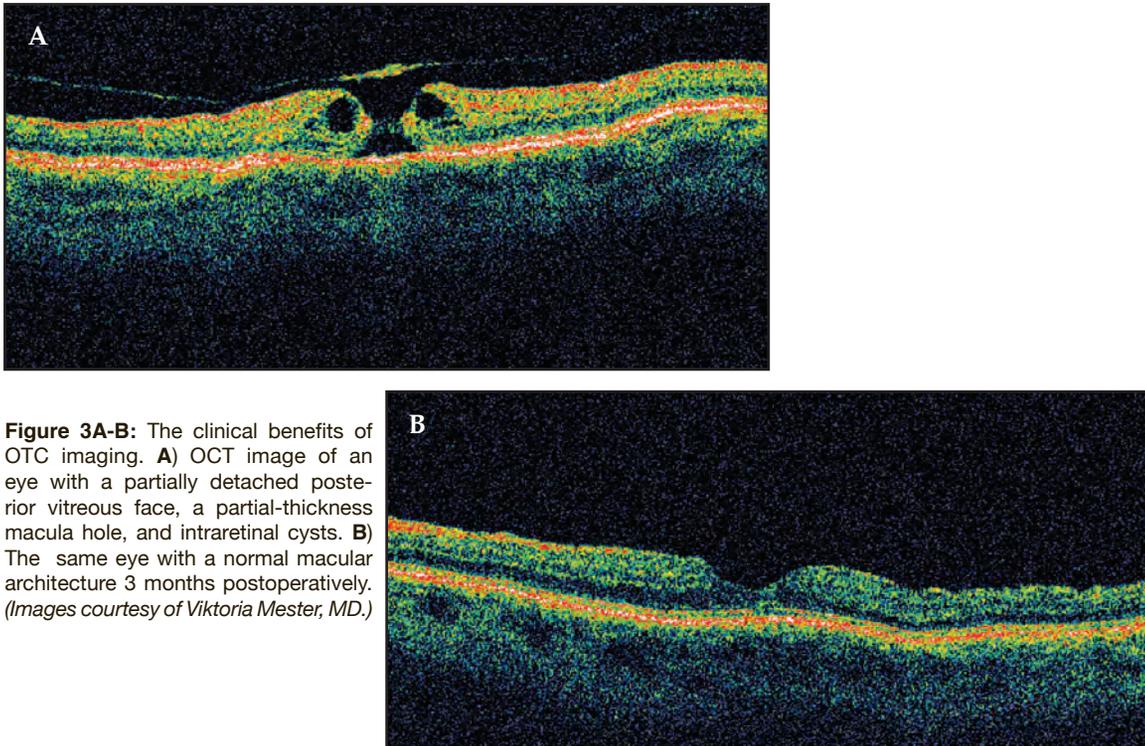


Figure 3A-B: The clinical benefits of OCT imaging. **A)** OCT image of an eye with a partially detached posterior vitreous face, a partial-thickness macula hole, and intraretinal cysts. **B)** The same eye with a normal macular architecture 3 months postoperatively. (Images courtesy of Viktoria Mester, MD.)

Fluorescein angiography. Although it is an invasive diagnostic tool, it is still the only method to show vascular leakage (Figures 4A and B).

Electrophysiology. The multifocal electroretinogram shows marked central depression in eyes with foveal dysfunction (Figure 5); the test is uncommonly utilized in clinical practice but is a good method to follow macular function changes following surgery.

Counseling

Once the diagnosis has been established, it is the ophthalmologist's responsibility to explain the condition to the patient. The ophthalmologist must describe the natural history – typically one of continual dete-

rioration, although of variable speed –, and the benefits as well as risks of surgery, giving specific numbers (percentages) if these are available. In an ideal situation, it is the patient who chooses to undergo treatment, not the ophthalmologist. (**Author's Note:** It is unacceptable for the ophthalmologist to set an arbitrary limit below which he would refuse to undertake surgery. It is often said by these ophthalmologists that “I will not operate on a macular hole unless vision is 20/40 or worse”; such – scientifically unjustified – statements do not take into consideration that one individual's needs and desires can greatly differ from another person's. Surgery is not done on a macular hole but on an individual who has a macular hole).

The patient must understand that even if the visual symptoms are minimal, certain

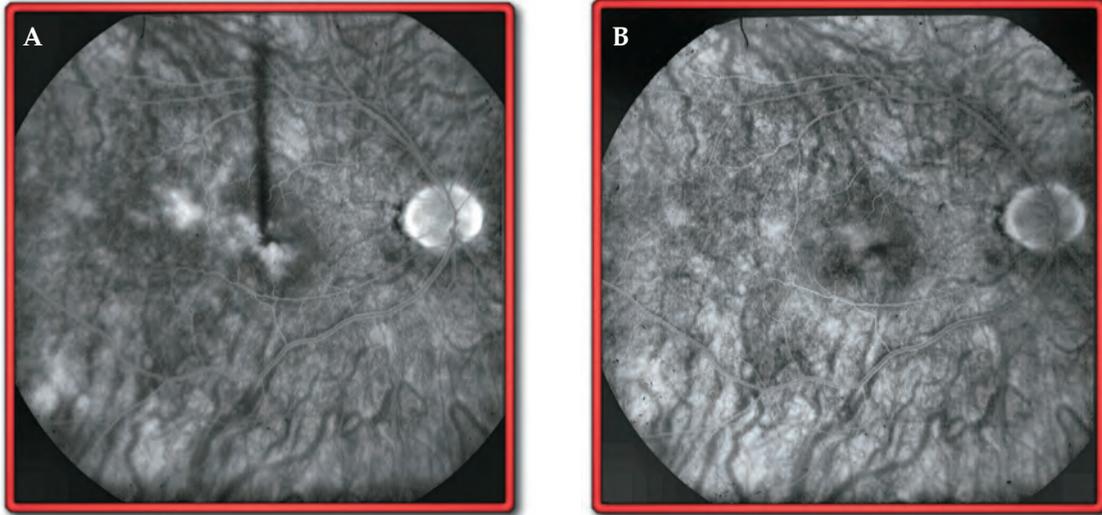


Figure 4 A-B: Macular Pucker fluorescein angiogram. **A)** Extensive fluorescein leakage from retinal blood vessels in the late phase, secondary to traction forces of epimacular proliferation, preoperative. **B)** Macular pucker fluorescein angiogram, postoperative. Fluorescein leakage has now largely resolved six weeks after removal of all epimacular proliferation.

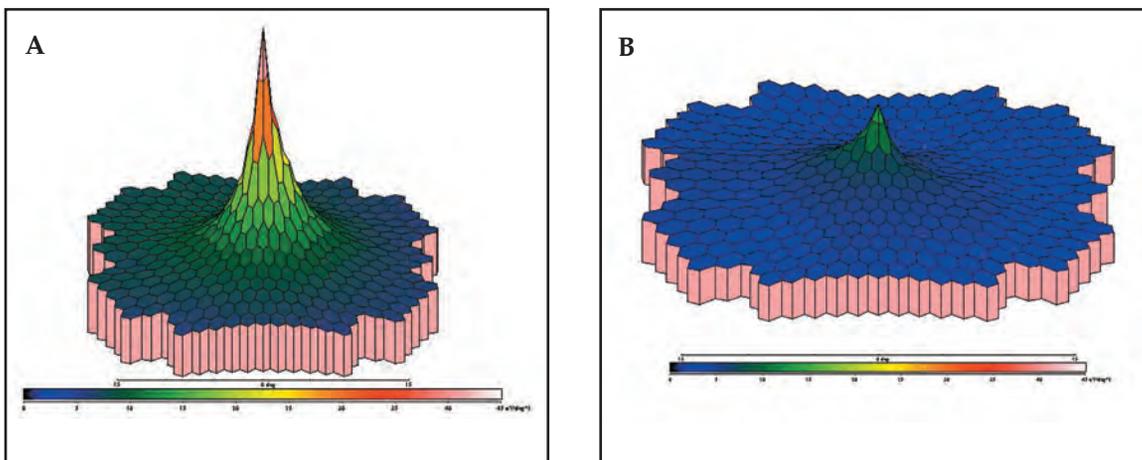


Figure 5 A-B: **A)** Multifocal Electroretinogram (MFERG), normal. Note the high peak at the foveola, with gradual taper in the surrounding foveal and macular tissue. **B)** Multifocal Electroretinogram (MFERG), abnormal, macular pucker. Note the severely depressed central peak corresponding with foveal dysfunction secondary to EMP traction.

complications of traction maculopathy, such as cystoid edema, may cause damage that can prove irreversible if the intervention is delayed indefinitely.

Treatment

The only predictable and effective method to treat patients with traction maculopathy is pars plana vitrectomy. Until a few years ago, all operations would have been performed using 20 g systems, but today many surgeons elect to use smaller g instrumentation (23 or 25 g). (**Author's Note:** Technical details related to gauge are not discussed in this chapter). In addition, when using the term “complete vitrectomy” here, it rarely means that a radical peripheral vitrectomy with scleral indentation is done; rather, the vitreous base is left intact in most eyes.

For further details, see the individual conditions described below.

Vitreomacular Traction Syndrome

Depending on the severity of the condition, the patient may notice a distinct drop in visual acuity or a severe drop as well as mild to significant distortion (metamorphopsia). An incomplete detachment of the posterior hyaloid face (PHF) is the cause (Figures 6 and 7), but the vitreous may also be completely attached with firm connection to the internal limiting membrane (ILM), pulling on it as the degenerating vitreous moves. Epimacular proliferation may also be present.

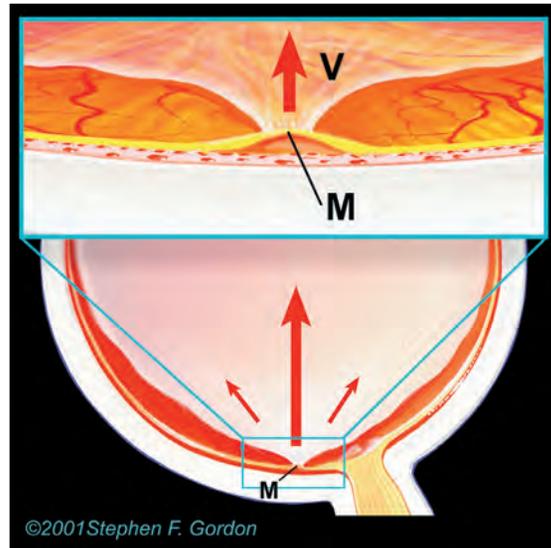


Figure 6: Vitreomacular Traction Syndrome. The top view shows how the vitreous (V) may exert anterior posterior traction (arrow) on the macula (M) as a consequence of forward movement of the vitreous coupled with persistent attachment of cortical vitreous at the macula. Below shows the focally intensified forces (arrows) of the vitreous traction on the macula (M) as exerted by the mass of the entire body of the free moving vitreous.

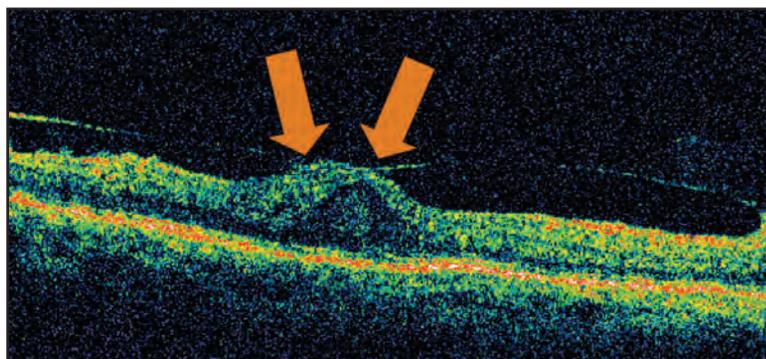


Figure 7: OCT imaging of vitreomacular traction syndrome. The partially detached posterior vitreous face shows strong adhesion to the retina centrally (arrows), causing a dramatic change in the macular contour. (Image courtesy of Viktoria Mester, MD.)



The OCT may show the actual PHF as well as its attachment to the retina.

Treatment: Removal of the entire vitreous, especially posteriorly (see below in more detail). This is greatly aided by the use of triamcinolone acetonide (TA) as a marker to show the vitreous that otherwise would remain invisible. It is highly recommended to remove the ILM as well, both to make sure that no vitreous is left behind and also because the ILM may also be pathological.

It is helpful to stain the ILM before removal; this makes the procedure less traumatic to the retina, less stressful to the surgeon, and not only reduces the time needed for removal but also allows it to be more complete (see below for details).

The surgeon should consider indirect ophthalmoscope-delivered encircling laser prophylaxis (Figure 8) to almost eliminate the major risk of vitrectomy for traction maculopathy: retinal detachment from a peripheral break.

Prognosis: If surgery has been timely, excellent outcome is expected; if, however, the condition has been present for an extended period of time and the vision is severely affected, the functional result will not match the anatomical one. The patient must be made aware of this during counseling (see above).

Cellophane Maculopathy

(Author's Note: "Preretinal gliosis" is another term occasionally, but incorrectly, used. As described above, cellophane maculopathy

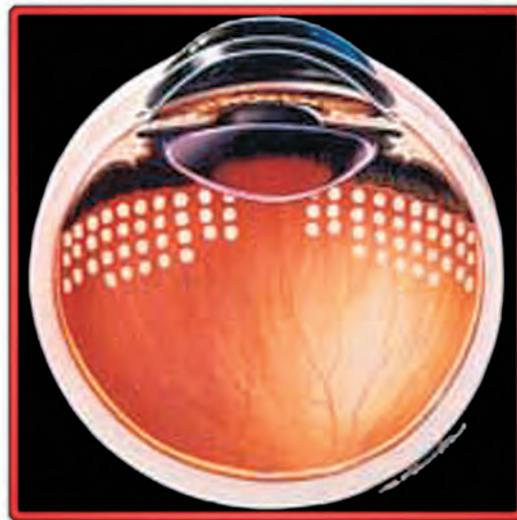


Figure 8: Indirect Ophthalmoscope (IDO) Laser Encircling Prophylaxis.

is a mild variation of an epimacular proliferation but still interpreted as a distinct entity since no membrane is visible on the retinal surface. With the retinal traction involving only the superficial retina (Figures 9 and 10, this condition can be interpreted as a mild form of an epimacular proliferation. There is no visible membrane present (it is also possible that it is just too thin for detection with current technology), but cells seeding the surface do cause anatomically visible changes. Careful examination is necessary to detect the fine "wave formation" of the retinal surface; often this is best seen intraoperatively, once the retina has been stained. Of the four conditions mentioned herein, this is the least urgently in need of treatment.

Treatment: If the patient is sufficiently bothered by the metamorphopsia caused by contracted ILM (resembling wrinkled

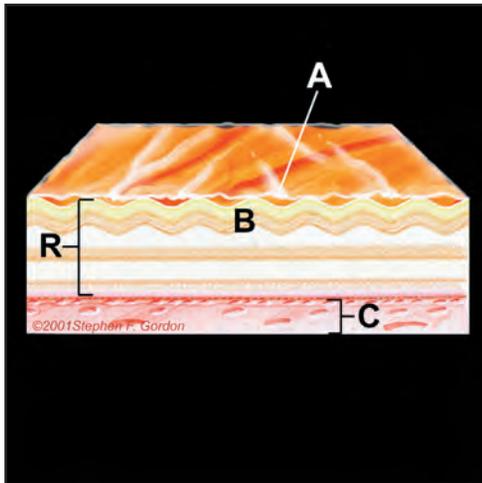
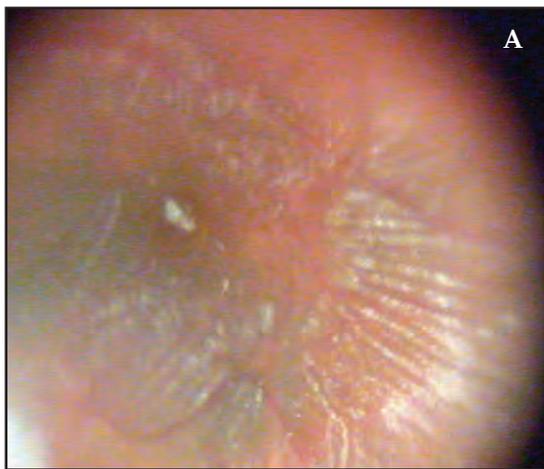


Figure 9: Anatomy of Cellophane Maculopathy. This conceptual section view shows the anatomy of cellophane maculopathy, which has a clinical appearance similar to that of wrinkled cellophane. The internal limiting membrane (A), as a single sheet, is contracted by modest EMP, not removable as a separate layer. This contraction is sufficient only to affect the immediately underlying neurosensory retina (note distorted inner layers of retina - B). Full thickness of retina (R) and choroid (C).



cellophane and giving the condition its name), a complete vitrectomy is recommended with removal of the ILM (see above).

Surgical Steps of Complete Vitrectomy

(**Author's Note:** Variations in surgical technique exist; the authors simply describe here their own technique without

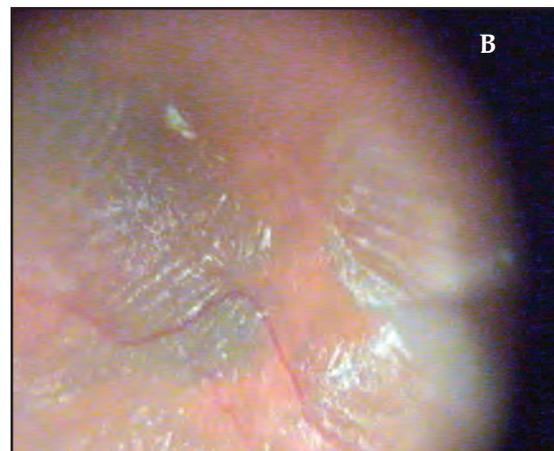


Figure 10 A-B: Cellophane maculopathy. (A and B). Different areas of a macula with fine wrinkling of its surface. The negative staining with indocyanine green shows the presence of cells and perhaps a fine, invisible membrane on the ILM; use of TA, however, enhances fold detection. In the right lower corner of Fig. 10B, the bent MVR blade used to incise and peel the ILM can be ascertained.



the intention of claiming its superiority over other techniques).

- Remove the central vitreous.
- Inject a minimal amount (0.1 ml) of filtered TA to verify the presence and geography of the PHF.
- Lift the undetached PHF with aspiration using the vitrectomy probe or engage and lift it with a bent microvitrectoretinal (MVR) blade. Do not carry detachment of the PHF too far to the periphery as it risks retinal break formation with subsequent development of retinal detachment.
- Remove the remaining vitreous.

For the surgical steps of ILM removal, see the section on macular hole (below).

Prognosis: Usually excellent, unless severe macular edema has developed and the treatment has been delayed for too long.

Epimacular Proliferation (EMP, Macular Pucker)

(Author's Note: The term “macular pucker” implies that the full thickness of the tissue is involved; the term “epimacular proliferation” refers to the underlying cause of the condition. In clinical practice, the two terms are used interchangeably as one refers to the cause and the other to the effect). An asymptomatic EMP is detectable upon careful examination in over 6% of persons over the age of 50 years; an estimated 15% of the cases ultimately become symptomatic.

The condition is characterized by proliferative cells forming a visible membrane on the ILM (Figure 11), causing full-thickness macular effects; inner folding, vascular distortion, leakage, macular edema, and cystic changes are characteristic consequences. The membrane may have a discernible edge or it may gradually “disappear” from recognition at its border. The visual complaint may arise from the distortion of the macula or from the opaque nature of the membrane itself.

Treatment: Removal of the vitreous, the epimacular proliferation, and, preferably, the ILM. **(Author's Note:** Some surgeons prefer removal only the vitreous directly in front of the macula, leaving most of the vitreous in situ (“minimal” or “core” vitrectomy). Yet another, small group of surgeons advocate removal of the EMP without performing any vitrectomy “non-vitreotomizing vitrectomy”). Peeling of the ILM is not an essential step for the removal of the EMP, but it is helpful for two purposes: making certain that no part of the EMP is left behind; and to virtually eliminate the risk of re proliferation, which is otherwise expected in 5-10% of the cases. During removal of the EMP, the surgeon must keep in mind that the membrane may have several layers, and failure to start with the outmost layer can extend the procedure’s time, risking photic maculopathy. Finally, the surgeon should not be hasty even when the membrane gives easily: it may have strong connections to the retina in unexpected areas, risking harm to critical macular tissue. **(Author's Note:** The fovea is identical to what is called in American football the “red zone”).

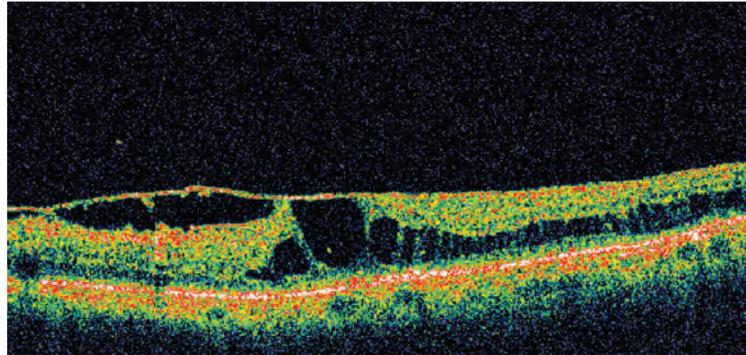


Figure 11: OCT imaging of an epimacular proliferation. The thick membrane causes traction; the vascular leakage leads to macular edema, which eventually becomes cystic. (Image courtesy of Viktoria Mester, MD).

Surgical Steps of EMP Removal

(**Author's Note:** Variations in surgical technique exist; the authors simply describe here their own technique without the intention of claiming its superiority over other techniques).

- Remove the entire (core) vitreous (see above).
- Consider staining the EMP if its anatomy is unclear – although rarely necessary, staining does have tangible benefits, especially for less experienced surgeons. A commonly used stain is trypan blue. (**Author's Note:** Alternatively, stain the ILM with indocyanine green (ICG) to show areas of no staining, which is caused by the presence of the EMP).
- Carefully examine the characteristics of the membrane: thickness, size, vascularization, adherence etc.
- Design your removal tactics, deciding whether:
 - You want to use a centripetal (towards the center) or centrifugal (starting in the center) technique of advancement, or a combination of the two (Figure 12);
 - You want to find an edge first to use direct-grabbing with forceps;
 - You want to create an edge (for which the Tano membrane scraper may be useful) first;
 - You prefer one type of forceps over another.
- Carefully lift the membrane, but remember to move your hand in a more-or-less retina-parallel plane to avoid exerting too much anteroposterior traction on the retina but also avoiding “bumping” into the retina by keeping too short a distance from it. (**Author's Note:** This is why a steady hand is needed, the surgeon must have a plan (surgical tactics) already established, and have a firm grab of the membrane before actual peeling occurs). Similarly,

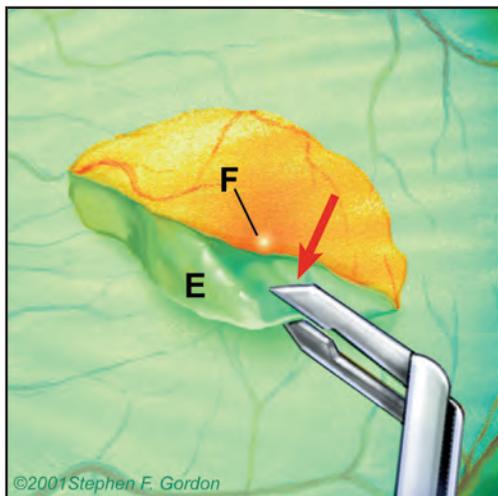


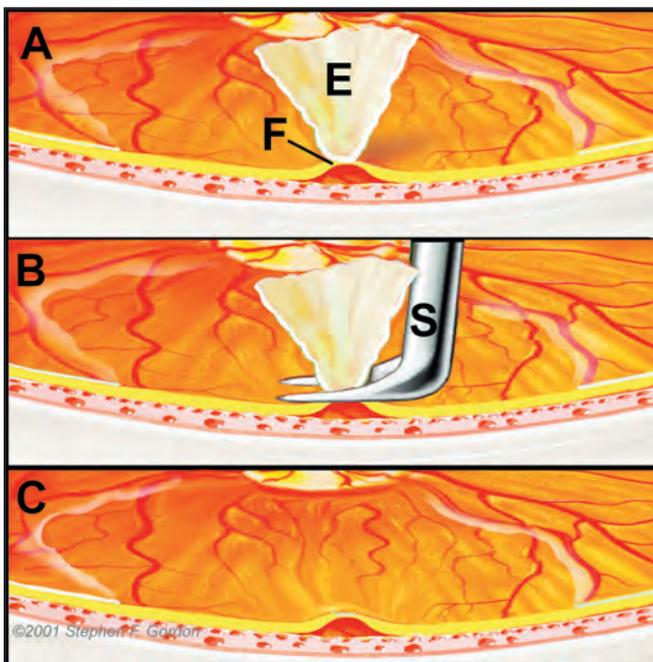
Figure 12: Epimacular Membrane (EMM), Radial Peel. The epimacular membrane in macular pucker is often firmly adherent to the fovea, and especially in long standing cases with cystic foveopathy, has the potential to tear the fovea if peeled radially. As shown here, the EMM (E) has been peeled radially across (arrow) the macular area and torn the fovea (F). Unfortunately, this complication cannot be completely anticipated since, unlike in maculorhexis, the fovea cannot be viewed except from the peeled side.

extra caution is warranted when peeling the membrane over cystic areas, to avoid unroofing of a cyst.

- If too strong a vitreoretinal connection is encountered, consider amputating the membrane here with retina-parallel scissors or the vitrectomy probe, rather than force the separation (Figure 13A-C).
- See below for details of ILM removal.

If the epimacular membrane is not too large or thick, an alternate technique is to remove it and the ILM together as a single piece (“en-block resection”).

Prognosis: The final postoperative visual acuity shows an improvement of two or more lines in over 80% of treated eyes, with 25-50% achieving $\geq 20/40$ vision. On average, the operated eye can be expected to regain approximately half of its lost visual acuity. Equally importantly, successful treatment avoids further anatomic and functional deterioration. Thus, with the substantial improvements in the efficacy and safety of macular surface surgery in recent years, earlier intervention may



Figures 13 (A-C): Epimacular Membrane (EMM) (Adherence after Maculorhexis). (A) Occasionally a firm foveal adherence of the EMM will result in non-separation during maculorhexis. The peeled membrane (E) floating above the fovea (F) can then be reduced by Morris/Witherspoon scissors and meticulously peeled from any side, or amputated (B) just above the fovea with Morris/Witherspoon horizontal scissors (S) held flush with the fovea as shown. (C) Shows the end result of the removed EMM.

reasonably be considered even for eyes with reading vision if cystic foveopathy portends future deterioration (see above) or in the presence of large disparity between the Snellen visual acuity and the MNREAD results.

Macular Hole

A full-thickness defect in the fovea is formed (Figure 14), which usually expands over time, coincident with the development of a surrounding cuff of subretinal fluid. Tangential traction may be present in the form of cortical vitreous and/or minimal fibrosis on the ILM surface (Figure 15). Patients with macular holes of stages 2 through 4 are commonly operated on, but results of surgery for stage 1 (impending) holes are also encouraging even if this indication remains somewhat controversial. (**Author's Note:** The natural history (i.e., spontaneous closure rate) of this condition is unknown. Despite initial reports of success with adjuvant therapy, it is now rarely employed; rather, surgeons routinely peel the ILM to improve the anatomical and

functional outcome, and reduce the risk of recurrence.

Treatment: Removal of the vitreous (see above), the epimacular proliferation (see above) if it is present, and, preferably, the ILM, followed by indirect ophthalmoscopic encircling laser prophylaxis (see above) and gas tamponade (see below). (**Author's Note:** Some surgeons prefer removal only the vitreous directly in front of the macula, leaving most of the vitreous in situ ("minimal" or "core" vitrectomy). Yet another, small group of surgeons advocate removal of the EMP without performing any vitrectomy "nonvitrectomizing vitrectomy"). The rationale to remove not only the hyaloid from above the macular hole but also the ILM is based on the understanding that tangential, in addition to anteroposterior, traction also plays a role in the development of the macular hole.

There are several controversial issues regarding the basic philosophy of surgery, such as:

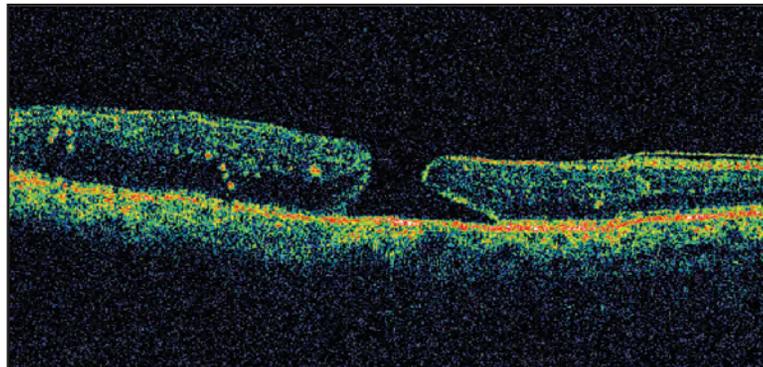


Figure 14: OCT imaging of a full-thickness macular hole. This image shows the contribution OCT technology makes to our understanding of the complexity of this disease: this hole's size is more controversial to measure than it would be based on slit microscopy. (Image courtesy of Viktoria Mester, MD).

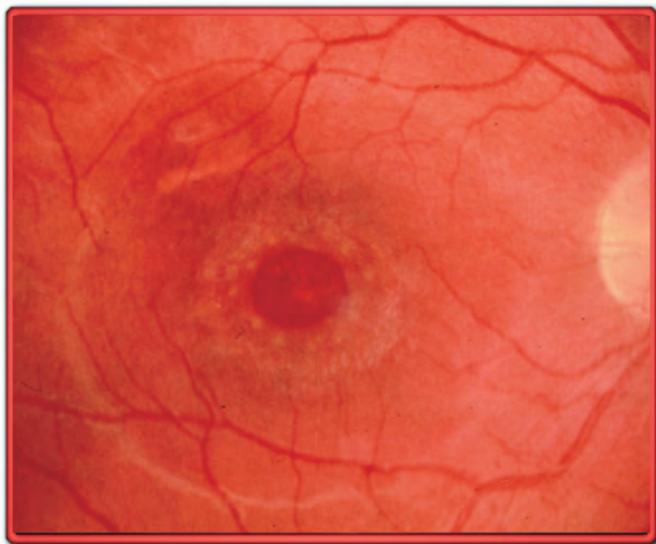


Figure 15: Macular Hole, Stage 4. A typical stage 4 macular hole with distinct edges, complete posterior vitreous detachment, and subtle EMP. (Photo courtesy Mr. John Bishop).

- The need to routinely make the patient pseudophakic during the same procedure or do the cataract extraction/intraocular lens implantation as a preceding or secondary operation. (**Author's Note:** When mentioning the patient pseudophakic, we refer to those who already lost most or all of their accommodative power.);
 - The need to stain the ILM;
 - The type of stain to utilize. (**Author's Note:** While ICG is ideal to stain the ILM in eyes without a macular hole, it has been reported to cause toxicity in eyes with a macular hole where the dye can easily get under the retina. It is therefore recommended to either utilize another dye (e.g., trypan blue) or plug the macular hole with viscoelastic and limit both the dye's concentration and its duration in the eye.);
 - The need for ILM removal in every vs. only in selected cases;
 - The area of ILM removal: restricted to the immediate vicinity of the hole vs. up to the vascular arcades;
 - The need to use longer-term gas tamponade vs. only air;
 - The need to use silicone oil as a tamponading agent;
 - The need to position the patient postoperatively for an extended period vs. only for one or only a few days.
- Lacking a clear answer in the literature to these questions, we simply describe our various methods of ILM removal with brief comments on some other techniques.

ILM Removal Techniques

(**Author's Note:** ILM peeling" or "ILM maculorhexis" (a term coined by Drs.



Robert Morris and C. Douglas Witherspoon), are commonly used phrases to describe the procedure).

Instrumentation

Forceps

The first issue to determine is whether the surgeon prefers to incise the ILM before grabbing it. The bent MVR blade gives greater control of the depth than the forceps (remember, the ILM is 2-4 μ thick) and allows a more precise initial tearing (Figure 10B).

Next, the surgeon must decide what type of forceps to use. A forceps with a large platform (end-gripping) reduces the risk of shredding the ILM but blocks the surgeon's direct viewing of the forceps' action. The Morris/Witherspoon "full-view" forceps has a small platform and an angle as well as a hollowed shaft, allowing ideal visual control of the procedure, but can tear the ILM a little more easily.

Tano Membrane Scraper

Although some surgeon use this instrument to not only create the initial break in the ILM but to actually complete the peeling with it, this a very dangerous procedure since the soft silicone tip of the scraper is coated by diamond crystals that can easily injure the retinal nerve fibers in areas already denuded of the ILM.

Cannula (FILMS® Technique)

(**Author's Note:** The term FILMS® stands for Fluidic Internal Limiting Membrane Sepa-

ration, a technique developed by Drs. Robert Morris and C. Douglas Witherspoon).

A specially designed microcannula is inserted under the ILM and viscoelastic is injected to simulate ILM separation, simulating the process found in eyes with a submembranous hemorrhagic macular cyst in Terson syndrome.

Surgical Techniques

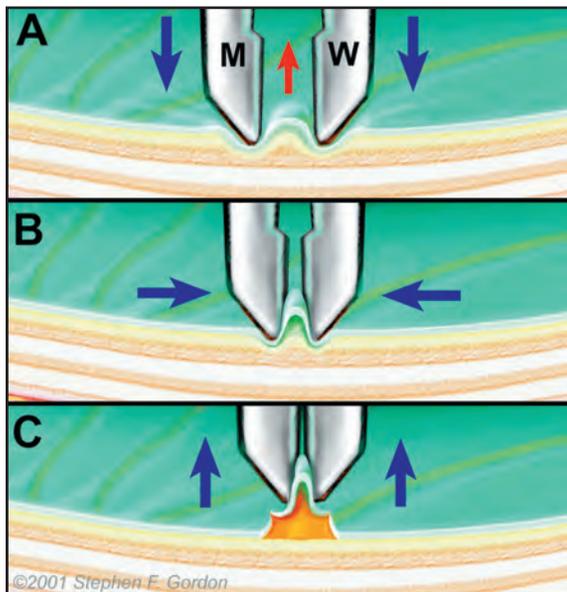
The "keyhole" Technique

(**Author's Note:** The "keyhole" technique is ideally done using the Morris/Witherspoon ILM forceps (Synergetics, St. Louis, MO) because it allows continual visualization of every detail of the peeling).

The initial opening of the ILM is performed using the "pinch technique".

The forceps is inserted in an oblique, vertical orientation to the retina. With the forceps slightly open, the retinal surface is contacted in an avascular region inside the arcade vessels, at 6 o'clock or 12 o'clock. As tissue contact occurs, the forceps jaws are closed and slowly elevated. The stained ILM is seen to rise as the forceps is slowly elevated with the ILM in grasp. If excessive movement of the surrounding retina is seen, the forceps is opened and the maneuver is repeated. An ILM break can easily be seen as the forceps is opened (Figures 16A through C).

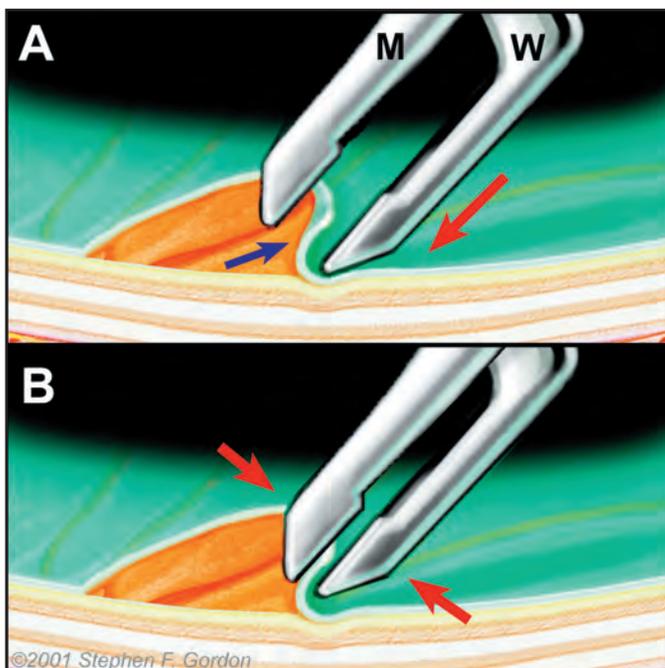
The ILM edge thus produced is then grasped by gently pushing down on the retina in an adjacent area (i.e., where the ILM "cover" is still preserved) with a slightly opened forceps jaw, causing the ILM edge to lift from the



Figures 16 (A-C): "Pinch Technique" for Creating an Initial Opening in the ILM. **(A)** A Morris/Witherspoon ILM forceps (MW) is inserted in an almost vertical orientation to the retina. With the forceps slightly open, the retinal surface is contacted in an avascular region inside the arcade vessels, at 6 o'clock or 12 o'clock to the macular hole. As tissue contact occurs, the gentle depression force downward (blue arrows) causes an upward counter movement of the ILM (red arrow) to a position between the tips of the forceps. **(B)** The forceps are closed (arrows) to grasp the ILM that has elevated between the tips of the forceps. **(C)** The forceps are slowly lifted (arrows) as the green ILM is seen to rise and gently tear. The forceps are opened, ready to regrasp an available edge of the ILM for subsequent peeling (see Figure 17).

retina and present itself for grasping (Figures 17A and B). The ILM strip is then gently peeled towards the macular hole, creating a

vertical ILM defect from the starting point almost to the hole (Figures 18 1A through 1C).



Figures 17 (A-B): Technique for Grasping the Edge of the ILM for Subsequent Peeling. **(A)** A Morris/Witherspoon ILM forceps (MW) is inserted just behind an edge of the ILM break. With the forceps slightly open, the retinal surface is contacted with the lower forcep. As tissue contact occurs, the gentle depression force downward (red arrow) causes an upward counter movement (blue arrow) of the ILM edge into a position between the tips of the forceps. **(B)** The forceps are closed (arrows) to grasp the ILM edge that has elevated between the tips of the forceps. Subsequent peeling can then take place.

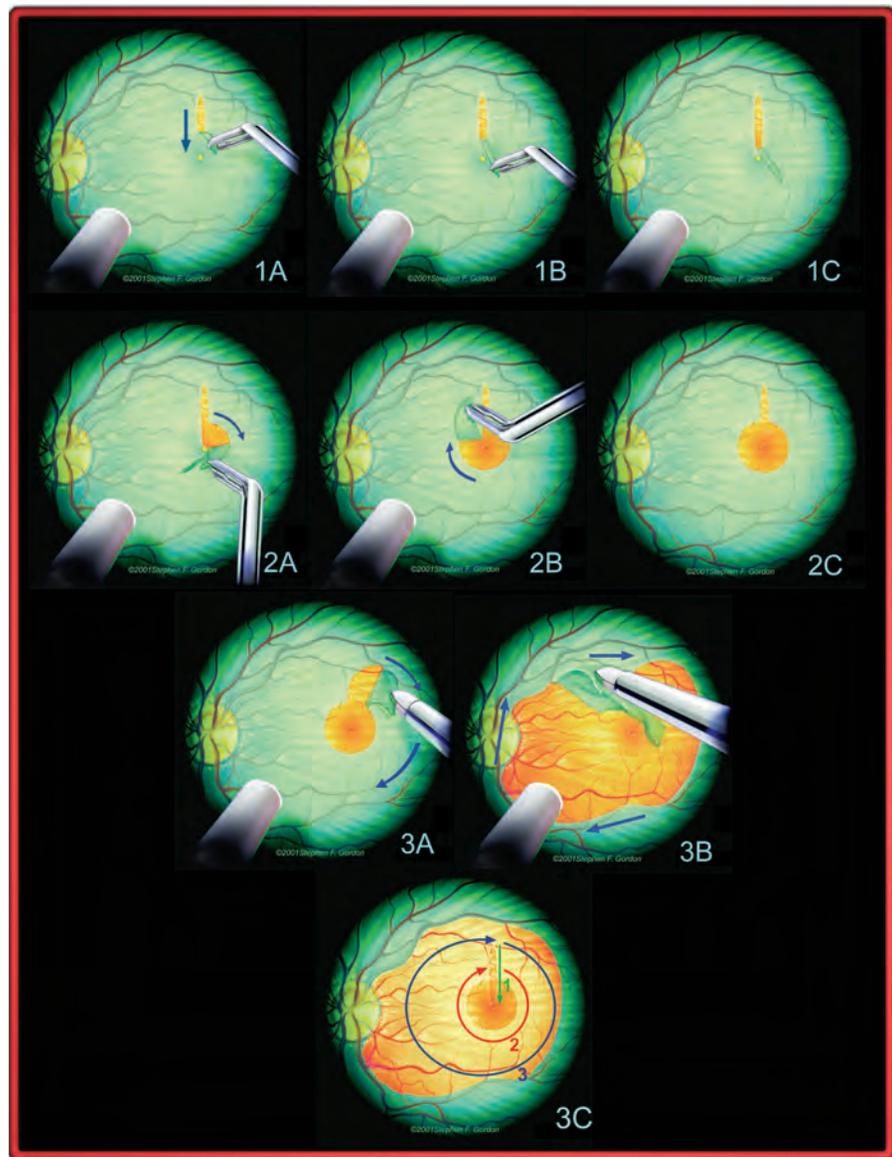


Figure 18: “Keyhole” Technique for Removal of the Internal Limiting Membrane (1A) The ILM is stained with ICG stain. The ILM is grasped with the Morris/Witherspoon ILM forceps and a strip is then gently peeled (arrow) towards the macular hole. (1B) The vertical ILM defect is created from the starting point almost to the hole, and released. (1C) Shows the extent of this initial peeled strip of ILM. (2A) The exposed edge is grasped, and a parafoveal rhexis is started with a circumferential movement (arrow) around the fovea. (2B) This parafoveal circumferential rhexis is continued (arrow), releasing and re-grasping as necessary. (2C) Shows the completed first full circle rhexis with ILM strip removed from the eye. (3A) The ILM edge is again grasped, and a peripheral maculorhexis is performed (arrow). (3B) This rhexis is continued around (arrows) and the tissue is also removed from the eye. (3C) Final frame shows the pattern of ILM removal - 1-initial strip, 2-first circumferential peel, 3-second circumferential peel.



The ILM edge is again grasped, and a parafoveal rhexis is performed (Figures 18 2A through 2C). Finally, peripheral ILM maculorhexis is accomplished, and this tissue is also discharged from the eye (Figures 18 3A through 3C). The surgeon must pull the ILM toward, never from, the hole, to avoid enlarging it and causing further damage.

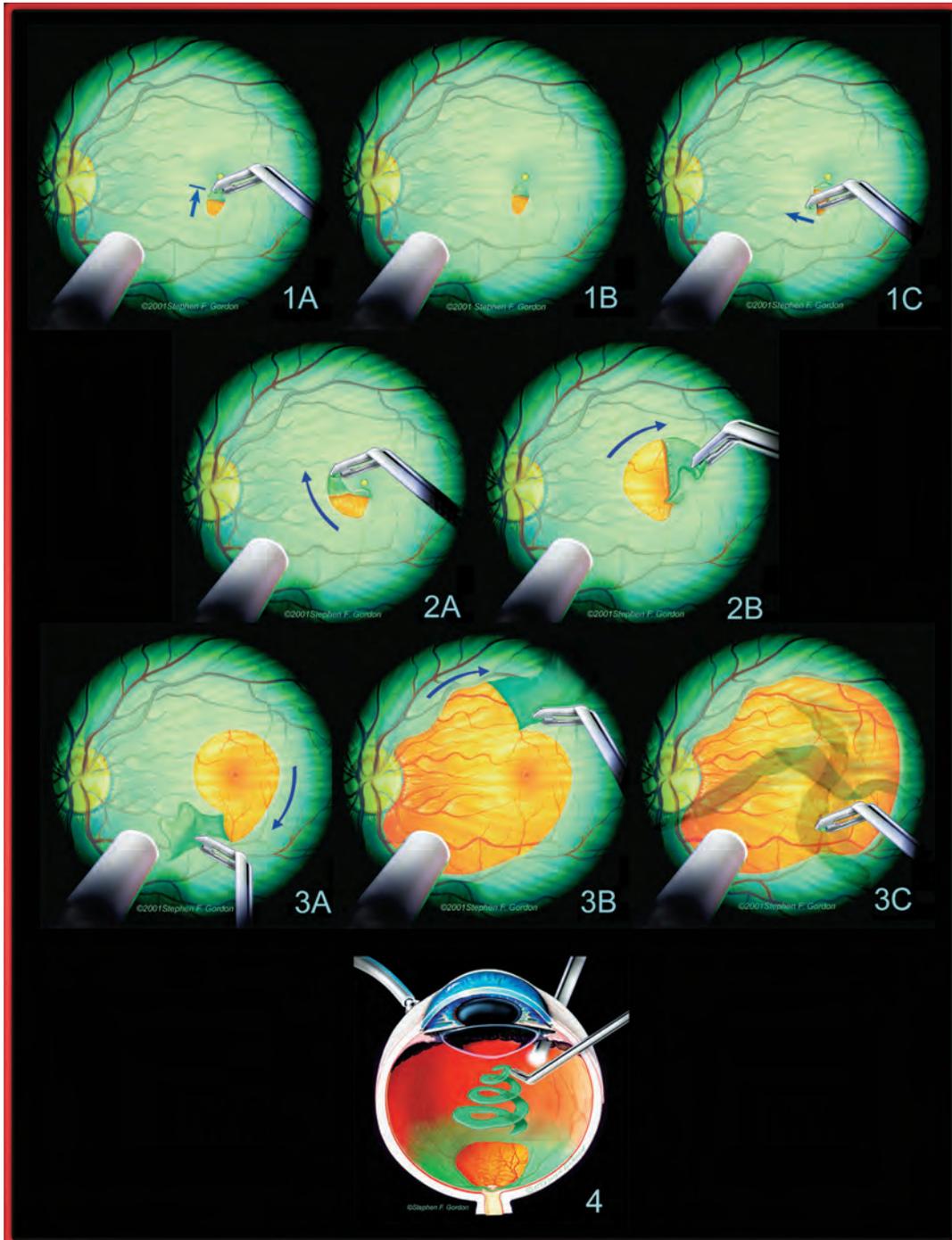
As an alternative, a modified keyhole-maculorhexis can be performed, by grasping an edge of the vertical strip peripherally and proceeding circumferentially in a single maculorhexis.

The "Apple-Peel" Technique

The stained ILM is grasped 500-700 microns above or below the fovea, and a thin

strip is peeled radially, almost to the fovea, and released. The exposed edge is then grasped at its midpoint, and a parafoveal strip of ILM is started with a circumferential movement around the fovea. This parafoveal rhexis is continued, releasing and re-grasping as necessary, until the rhexis is approaching a full circle around the fovea. An outward force vector is then intentionally applied so that the ILM strip expands outwardly in a continuous fashion. Re-grasping as necessary, this maneuver is continued until the macular ILM has been removed in a single strip, which is then removed from the eye, avoiding the need for multiple forceps removal and reinsertions (Figure 19).

Figures 19 (See Facing Page): "Apple Peeling" Technique for Removal of the Internal Limiting Membrane. (1A) The ILM is stained with ICG stain. The ILM is grasped with the Morris/Witherspoon ILM forceps 500-700 microns above or below the fovea, and a thin strip is peeled radially (arrow), almost to the fovea, and released. (1B) Shows the extent of this initial peeled flap of ILM. (1C) The exposed edge is then grasped at its midpoint, and a parafoveal strip of ILM is started with a circumferential movement (arrow) around the fovea. (2A) This parafoveal circumferential rhexis is continued (arrow), releasing and re-grasping as necessary. (2B) Shows the rhexis halfway around the fovea. (3A) Shows the rhexis approaching a full circle around the fovea as an outward force vector (arrow) is then intentionally applied so that the ILM strip expands outwardly in a continuous fashion. (3B) Re-grasping as necessary, this maneuver is continued (arrow) until the macular ILM has been removed in a single strip. (3C) Shows the single-piece ILM strip ready for removal from the eye, avoiding the need for multiple forceps removals and reinsertions. (4) Shows a conceptual view of the microforceps holding the single-piece removed ILM strip as removed from the retina. Note unstained area of retina from which this ILM strip was removed. Light is provided by an endofiberoptic and infusion via a separate infusion port.





The FILMS[®] Technique

The appeal of this technique is that it avoids lifting the retina while the ILM is separated from the rest of the retina. The viscoelastic fluid is injected underneath the ILM through a special 36 g microcannula whose proper placement is the most crucial element in the procedure; the microcannula is held in this plane while the surgeon momentarily (i.e., low pressure/flow) injects the viscoelastic (Figures 20 and 21); the injection force is controlled by the foot of the surgeon, thereby avoiding too much pressure that would disrupt the ILM. (**Author's Note:** The injection force controlled by the foot of the surgeon, requires proportional pressure, with the maximum set at a low level for

this maneuver). Following the creation of the initial bubble, the surgeon withdraws the microcannula to have visual confirmation of being in the correct plane (i.e., under the ILM and not under the retina). The microcannula is then reinserted and its slow advancement is coordinated with further viscoelastic injection. Finally, with an adequate size of ILM separation, the ILM is grasped with forceps and is removed.

Prognosis: A previously incurable disease, most macular holes are successfully closed today, and vision improves in all but the very chronic cases. Most clinicians routinely remove the ILM today, achieving macular hole closure rates of ~95%, 10% to 15% greater than without ILM removal ($p < 0.0001$).²

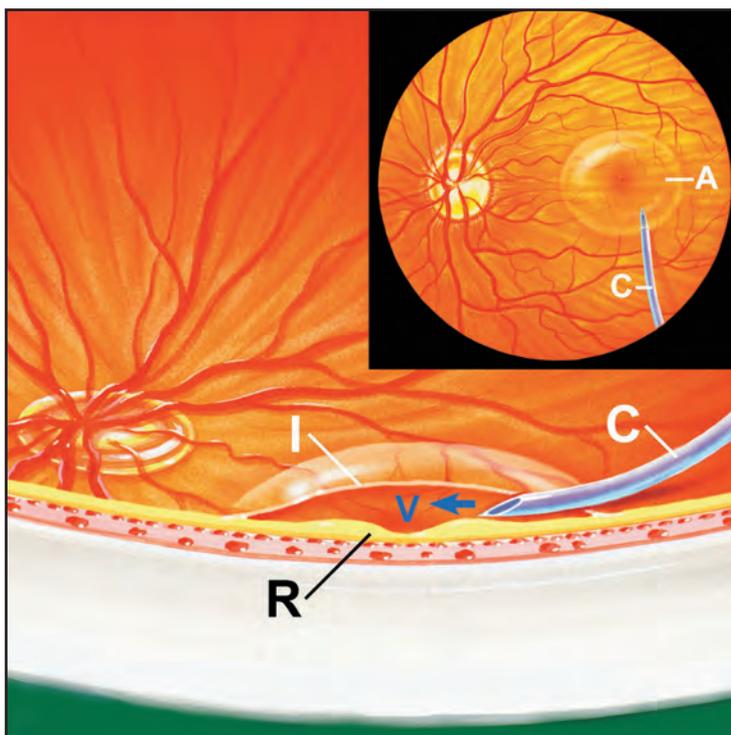


Figure 20: Schematic representation of the FILMS technique. See the text for details C: microcannula; I: ILM, R: retina; V: viscoelastic. (Art from Jaypee - Highlights Medical Publishers).

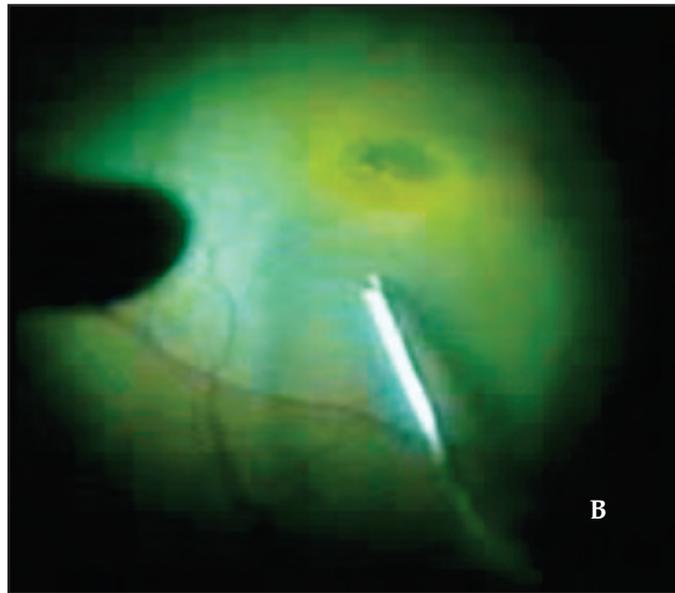
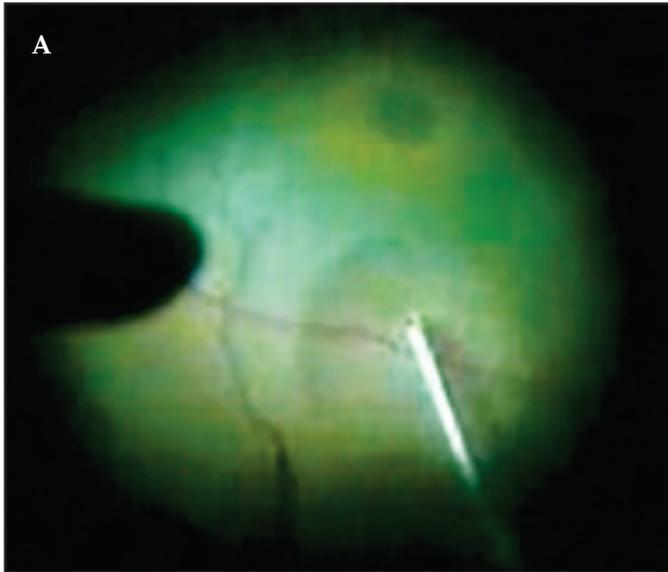


Figure 21 A-B: Intraoperative view of the FILMS technique. **A)** As illuminated by the endoscopic light source (seen on the left), the microcannula is inserted under the ILM to form an initial viscoelastic "bubble". **B)** As the bubble (and the microcannula) advance, the retina proper is pushed back (down) while the ILM is released at the hole's edge.

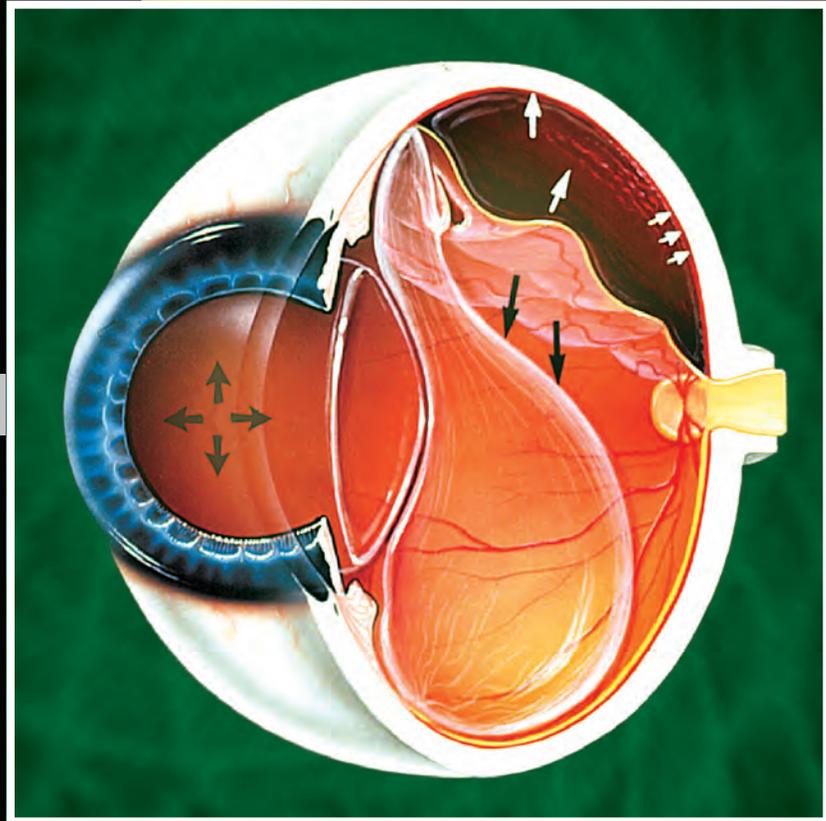


In summary, traction maculopathies, which used to interfere with the patients' visual performance, have now a high cure rate if timely vitreoretinal surgery is carried out. Removal of the ILM, either as part of the actual treatment or as a prophylaxis against recurrence, is usually performed for these pathologies today, and the list of indications is growing. (**Author's Note:** With our understanding of the pathophysiology of various maculopathies improving, (tangential) traction is increasingly identified as part of

the problem in many diseases; one obvious example is diabetic maculopathy). The surgical techniques are evolving, improving the results and reducing the associated risks.

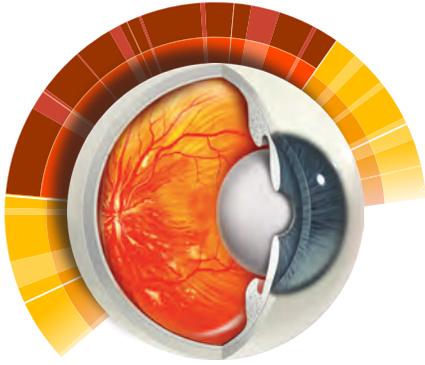
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Section 6

Retinal Detachment Surgery



23

Evaluation and Management of Retinal Detachment

RAFAEL T. CORTEZ, MD.,
GIAN PAOLO GIULIARI, MD

Retinal detachment was first described in the 1700s; however, it was not until the invention of the ophthalmoscope in the mid 1800s when significant advances were made in its diagnosis. At the beginning of the last century, Jules Gonin described the role of the retinal tear in the development of rhegmatogenous retinal detachment, which dramatically changed the treatment.

Characteristics - Relation to Procedure of Choice

Retinal detachments are some of the most time-critical emergencies encountered by ophthalmologists. There are several techniques available for uncomplicated rhegmatogenous retinal detachment surgery, such as the scleral buckle technique, scleral implants, pneumatic retinopexy, the Lincoff balloon technique, or a pars plana vitrectomy. The decision to use one of these therapeutic options is usually

based on various factors, such as the number, location and size of the retinal breaks, the condition of the crystalline lens, individual patient factors, such as the expected compliance with bodily positioning after the surgical procedure, the availability of the operating room, and the surgeon's preferences.

THE SCLERA BUCKLING PROCEDURE

This procedure, introduced in 1949 and subsequently modified, gained enormous popularity with the introduction of the binocular indirect ophthalmoscope in the 1950's. Besides being generally indicated in rhegmatogenous retinal detachment, this procedure is preferred in patients who have any of the following presentations: multiple tears that are distant from one another, grade "C" proliferative vitreoretinopathy (PVR,) greater inferior retinal breaks and questionable retinal breaks.



First Steps in Scleral Buckling

Precise location of the retinal breaks and a meticulous drawing of the fundus should be done before surgery (Figure 1). The pupil must be adequately dilated. Many retinal surgeons use local anesthesia, which in most cases is quite effective. A mix adds 150 units of hyaluronidase to a combination of 5 cc of 2% lidocaine and 5 cc of 0.75% bupivacaine. A total of 6 cc of this mixture is injected. This combination without hyaluronidase is also effective. Parabulbar or flush local anesthesia method may be used.

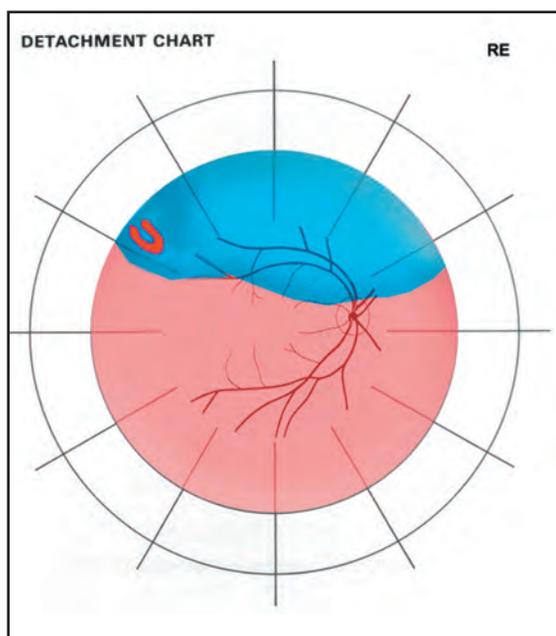


Figure 1: Color Diagram of a Retinal Detachment Chart. The retinal detachment characteristics are drawn in a specific chart using a well known color key among ophthalmologists. This chart includes the patient's name, date and the affected eye. The detached retina is colored in blue, the attached retina is colored in red and the causative retinal tears or degenerations are colored in red outlined with blue. (Art from Jaypee Highlights Medical Publisher).

During the procedure more anesthesia may be added with the use of a blunt cannula in the sub-Tenon's space. The anesthesiologist monitors the procedure closely and uses intravenous medication as needed.

The operative field is then prepared in the usual way. A Barraquer lid speculum is placed. The limbal conjunctiva and Tenon's capsule are pulled up with forceps and cut down to the sclera (Figures 2 and 3). If only one or two quadrants are to be buckled, the extension of the peritomy is limited (Figure. 2). Tenon's capsule is separated from the sclera by blunt dissection, and two

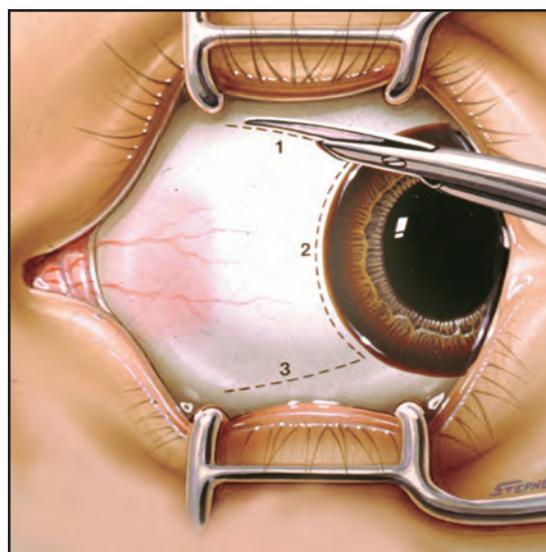
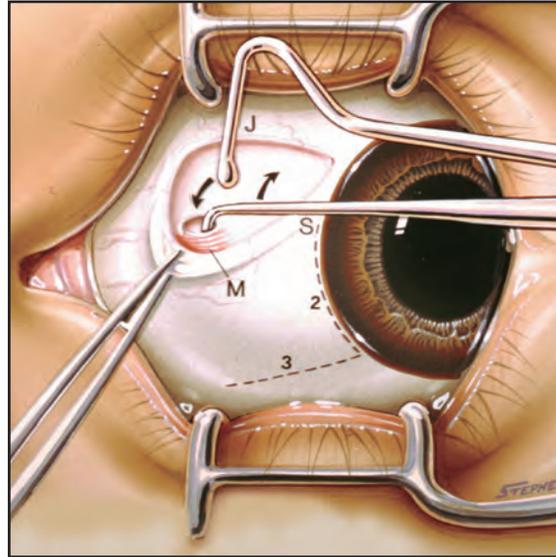


Figure 2: Conjunctival Peritomy and Radial Incisions in Conjunctiva and Tenon's. This surgeon's view of a right eye shows a radial wing incision (1) being made in the inferior nasal quadrant through the conjunctiva. Scissors are then used to create an incision in the anterior Tenon's capsule and conjunctiva to expose sclera near the inferior edge of the medial rectus (not shown). The limbal peritomy (2) and superior radial wing incision (3) will be performed after the muscle has been isolated in the following steps. (Art from Jaypee Highlights Medical Publisher).

Figure 3: Dissection of Tenon's and Muscle Isolation. A small Stevens muscle hook (S) is placed through the incision made in Tenon's capsule to hook the medial rectus muscle (M). A 2-3 Lester forceps placed at the limbus and used to fixate the eye during this maneuver is then removed (not shown). Next, a Jameson muscle hook (J) is placed behind the Stevens hook to replace it behind the muscle (arrows). The conjunctival incision is extended along the limbus (2) and the second radial wing incision is made in the superior conjunctiva (3). (Art from Jaypee Highlights Medical Publisher).



radial relaxing incisions are made (Figure 3). Three to four rectus muscles are usually isolated and strapped with 2.0 black silk to allow sufficient manipulation of the globe (Figures 4 and 5). To expose the posterior part of the eye, the conjunctiva and Tenon's capsule is pushed back with a cotton tip applicator.

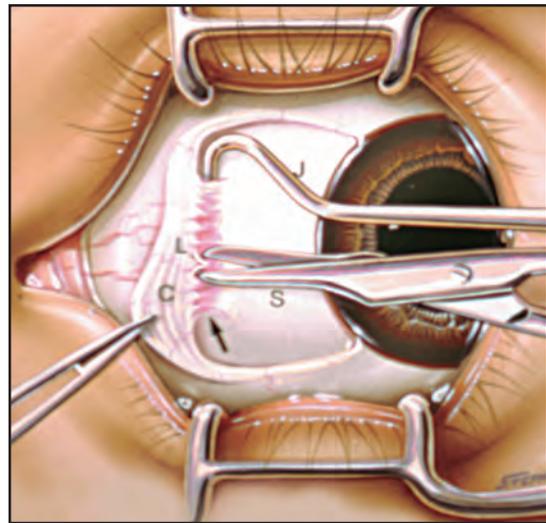


Figure 4: Rectus Muscle Isolation Technique. The conjunctiva (C) is reflected with forceps and check ligaments (L) that extend from the medial rectus muscle to the underside of the conjunctiva are removed with blunt and sharp dissection with scissors (S). Notice the Jameson muscle hook (J) behind the rectus muscle. Next, the intermuscular septum will be incised superiorly (arrow) to expose the tip of the muscle hook from behind the muscle. (Art from Jaypee Highlights Medical Publisher).

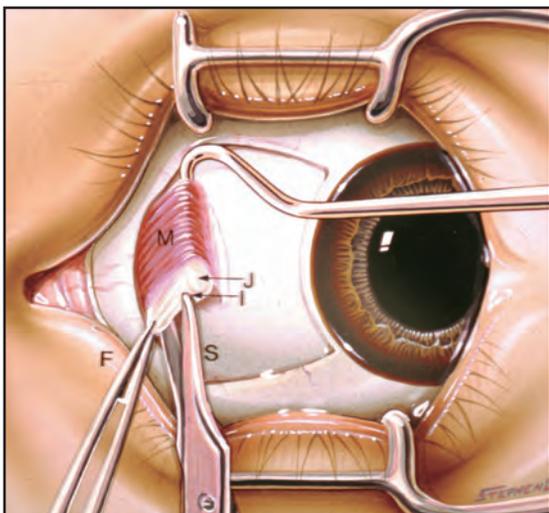


Figure 5: Final Stage in Muscle Isolation - Incising Intermuscular Septum. The superior nasal intermuscular septum (I) is bridged over the tip of the Jameson muscle hook (J) which protrudes from behind the rectus muscle (M) underneath the septum. The septum is grasped with a 2-3 Lester forceps (F). The septum is cut between the forceps and the tip of the muscle hook with Wescott scissors (S) as shown. This will expose the tip of the muscle hook from behind the muscle and septum. It is then verified that the entire muscle is engaged on the muscle hook (not shown). (Art from Jaypee Highlights Medical Publisher).

Identifying and Marking Retinal Breaks

All of the retinal must be identified. Marking the site on the external surface of the sclera that corresponds to the position of the retinal breaks is one of the most important steps in the procedure. Using the indirect ophthalmoscope for visualization and depressing the sclera with a scleral depressor or the wooden end of a cotton tip applicator, the area where the breaks are located is identified (Figure 6).

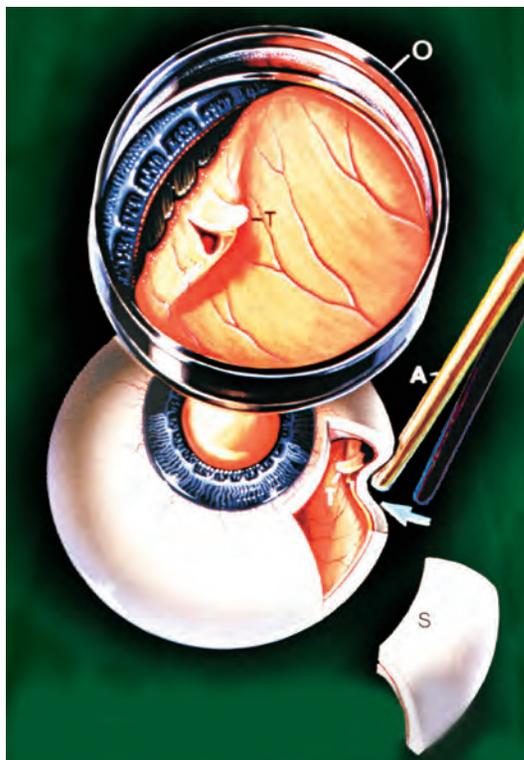


Figure 6: Method for Localizing and Marking Retinal Tears. This internal/external conceptual illustration shows how the site is marked on the external sclera that corresponds to the internal position of a retinal break. The indirect ophthalmoscope (O) is used for visualization while the sclera overlying the break is depressed (arrow) with the wooden end of a cotton tip applicator (A). A section of sclera (S) is shown removed to reveal a cross section of the scleral depression made directly external to the retinal tear (T). The corresponding surgeon's view of this depression is seen through the indirect ophthalmoscope lens (O). Temporary marks are then made on the sclera with a scleral marker. These temporary marks are then enhanced with a marking pen, superficial cautery or both. (Art from Jaypee Highlights Medical Publisher).

The surgeon makes temporary marks on the sclera with a scleral marker like the O'Connor marker or a Gass thimble. Finally, the surgeon enhances these marks with a marking pen, superficial cautery, or both.

The location marks depend on the characteristics of the breaks. For these cases the surgeon marks the posterior edge of small breaks and both ends of lattice degeneration whenever present (Figure 7). In cases in which a dialysis type tear is present, one should mark both edges, as well as the posterior extent to which the retina is likely to fall in a posterior direction (Figure 7). In large horseshoe tears, the posterior edge and both anterior horns are marked. Precise anterior and posterior localization of large horseshoe tears is very important since many of these tears are not radially oriented (Figure 7).

The surgical microscope may be used for external dissection. This is particularly important in re-operations and during the fluid drainage process. Using the microscope gives the surgeon greater control, illumination, and better visualization of tissue details. Although the surgeon also may use the surgical microscope for intraocular visualization during pars plana vitreous surgery, it is important to use the indirect ophthalmoscope (Figure 8), during buckling surgery for primary retinal detachments.

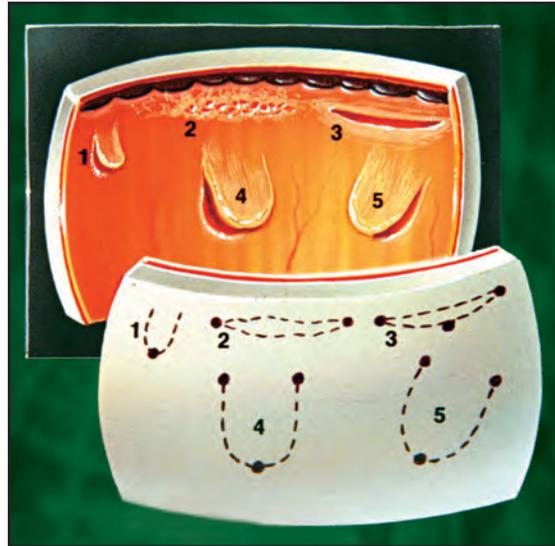


Figure 7: Localization Marks Depending on Retinal Tear Characteristics. In this series of figures, the dotted lines show the internal boundaries of the various types of retinal tears. The black dots show the proper location of the external scleral marks which are made to denote the boundaries of each. 1.) In the case of small breaks, the sclera is marked over the site of the posterior edge. 2.) In patients with lattice degeneration, both ends of the degeneration are marked on the sclera. 3.) The boundaries of a dialysis are noted by marking both ends and the posterior extent to which the retina will likely fall. 4.) For large horseshoe tears (Fig. 9 top), the posterior edge and the ends of the anterior flaps are marked externally on the sclera. 5.) Because such large tears may not be radially oriented as shown, it is important to note the anterior and posterior extent of the tear to delineate its full extent. (Art from Jaypee Highlights Medical Publisher).

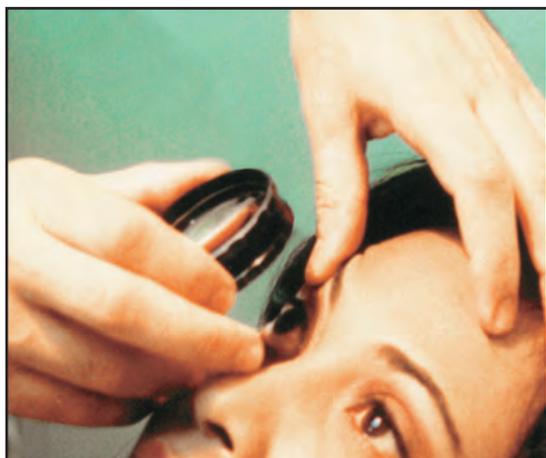


Figure 8: Indirect Ophthalmoscopy used for Observation of a Retinal Detachment. During planning of a pars plana vitreous surgery and or a retinopexy, it is important to use the indirect ophthalmoscope for localization of lesions and precise buckling implant procedure for a primary retinal detachments surgery. Please observe how the multicoat 20D lens is managed during the process of drawing the lesions implicated in the retinal detachment. (Art from Jaypee Highlights Medical Publisher).

After locating and marking the retinal tears, the surgeon must decide whether to use a localized explant and, if so, whether it should be radial or circumferential (see Figure 10 for a circumferential localized explant). He also chooses whether to use an encircling element alone or a combination of a radial and an encircling element (Figure 9). The type of material must also be selected.

Explants

Explants come in two basic types: silicone sponges, and solid silicone rubber, both of which may also vary in shapes and sizes (Figure 10). Solid silicone rubber is available in bands, straight strips, and symmetric and



Figure 9: Combination of Radial and Circumferential Explant Resulting in Excellent Tissue Re-Apposition. The surgeon has decided to make a buckle using a combination of radial (R) and circumferential (C) explants, as shown in the lower part of this figure. The position of a retinal tear and hole beneath these explants is shown as a dotted line. The tissue apposition internally is perfect as revealed by the path of the slit beam in the top figure. (Art from Jaypee Highlights Medical Publisher).

asymmetric tires. Some solid elements can be placed radially. Silicone sponges are either cylindrical in shape, 3 mm to 5 mm in diameter, or oblong with dimensions of 5 mm by 7 mm. Some sponges are grooved, with a channel in the middle. They are designed to be used in conjunction with an encircling silicone band. Segments of cylindrical sponges can be placed radially or circumferentially.



Figure 10: Different Types of Exopiants. Exopiants come in two basic types: silicone sponges and solid silicone rubber. Samples of each are shown in place on the globe and in cross section. As shown in figure above, solid silicone rubber is available in bands (A) both wide and thin (H), in straight strips (B), asymmetric (C) and symmetric (D) tires. Silicone sponges are shown below, as follows: cylindrical (E), or oblong (F). Sponges can be grooved (G) for placement beneath a band (H). Segments of sponges can be placed circumferentially (G) or radially (I). (Art from Jaypee Highlights Medical Publisher).

Selecting the Exopiant

The best exopiant to use depends upon the characteristics and the extension of the retinal pathology, the volume of subretinal fluid, and the amount of vitreous traction. The surgeon may choose an encircling exopiant in the following types of cases: retinal detachments with multiple breaks, aphakic or pseudophakic eyes, the presence of high myopia, extensive areas of lattice degeneration, PVR grade B or greater, giant tears, and eyes with very thin sclera. The surgeon may choose one or more from a great variety of elements, such as 41 or a 240 band combined with a grooved silicone strip or tire in most cases; occasionally, he will combine a 240 band with a grooved 6.5 mm sponge, in which case its circumferential length depends upon the extent of the retinal pathology (Figure 11).

Segmental circumferential buckles are indicated in closely spaced retinal breaks in the absence of other retinal pathology. Radial exopiants are preferred in cases with large horseshoe tears and relatively posterior tears. In our practice, with most horseshoe tears, we usually prefer a 4- or 5-mm silicone sponge cut in half, lengthwise, along the longitudinal axis of the tear. In cases in which the retinal pathology compromises more than one quadrant, and particularly, if it is associated with mild vitreous traction, one should consider using an encircling 240 solid silicone band (Figure 11).

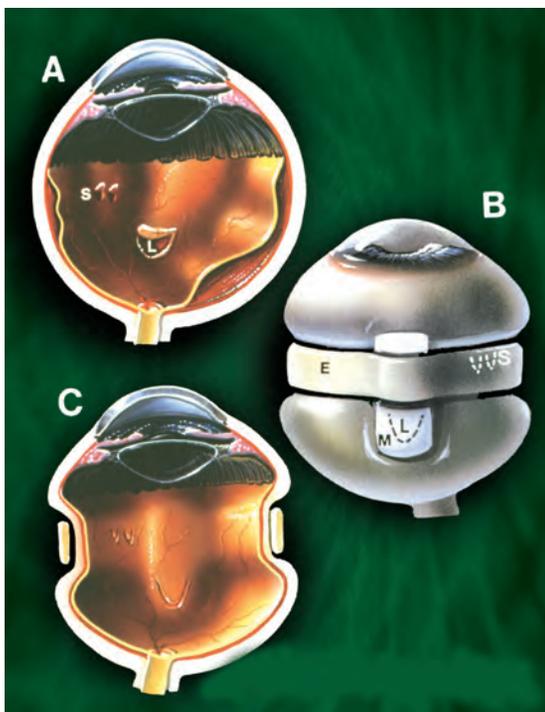


Figure 11: Indications for Radial Explant and Encircling 240 Degrees Solid Silicone Band. Figure A shows a large, relatively posterior horseshoe tear (L) and two small closely spaced equatorial tears (S). Figure B shows the radially placed silicone sponge (M). The interrupted lines in the area of the sponge (L) represent the location of the horseshoe tear beneath the explant. The radial sponge explant is shown combined with the encircling 240 degree solid silicone band (E). On the area of the encircling band, to the right, the interrupted lines in the shape of a V but marked (S) represent the location of the two small tears beneath the band. Figure C demonstrates the internal view of (B) showing reattachment of the retina and the appearance of the tears on the buckles with excellent apposition of tissues once the operation is completed. (Art from Jaypee Highlights Medical Publisher).

Sutures and Securing the Explant

The next step is the placement of the sutures to hold the explant in place to achieve an adequate indentation of the eye wall. Sutures of 5-0 polyester or nylon are placed with a half-curved spatula needle. The sutures should be inserted at approximately half the thickness of the sclera, and the suture bite into the sclera should be 3 mm to 4 mm in length. Suture placement depends upon the buckle being equatorial or radial. With a large, radially-oriented horseshoe tear (Figure 12), the distance between the marks at the anterior part of the tear is measured. This distance is extended by 3 to 4 mm. Sutures are then placed at these points. If the previous steps, have been performed properly, the tear should lie equidistant from the arms of the sutures. The sutures need to be 2 mm in front of the anterior marks and 2 mm posterior to the posterior marks in order to ensure a safe and efficient indentation of the sclera totally covering the tear (Figure 12).

For circumferential and encircling buckles, the goal is to have the tear, or the anterior and posterior marks of the tear, on the anterior slope of the indentation created by the buckle. This means that the distance between the suture bites must be twice as long as the distance between the anterior and the posterior marks of the tears. The tears have to be in the more peripheral half between these two points (Figure 13).



Figure 12: Suture Placement Technique for Radially Placed Exopiants. This conceptual illustration shows a section of the sclera with the proper placement of a radially placed sponge exopiant and a mirror view of the tear, detachment and ora serrata. Above, the foreground view (2) shows the external configuration of the exopiant (E) on the sclera (S) before tightening of the sutures. The image in the mirror (1-M) shows the corresponding internal configuration of the retinal detachment (R), retinal tear (T) and ora serrata (O). Note that the exopiant is centered over the retinal tear (2-dotted lines). The sutures are placed about 2mm anterior (A) to the anterior marks of the tear and also 2mm posterior (B) to the posterior marks. Laterally, the sutures are placed 2mm beyond (C) the anterior scleral marks. Overall, the tear should be between and equidistant from the arms of the suture.

Below, after tightening of the sutures (4), please observe the sponge exopiant (E) depressing the sclera externally in the foreground view. In the mirror view (3-M) showing the internal configuration, one can see the effect of this depression as the retina (R) is now reattached and the tear (T) is closed, flat and centered on the internally raised area (compare with (1)). (Art from Jaypee Highlights Medical Publisher).



Figure 13: Suture Placement Technique for Circumferential and Encircling Buckles. This conceptual illustration shows a section of the sclera with the proper placement of an encircling sponge type buckle. Above, the foreground view (2) shows the external configuration of the buckle (E) on the sclera (S) before tightening of the sutures. The image in the mirror (1-M) shows the corresponding internal configuration of the retinal detachment (R), retinal tear (T) and ora serrata (O). Note that the sponge is located slightly posterior to the tear, and its anterior and posterior marks. The sutures are placed such that the suture bites are twice as long (D") as the distance between the anterior and posterior marks of the tear (D'); the tear should be in the anterior half between the suture bites.

Below: following tightening of the encircling buckle sutures, notice the buckle (E) depressing the sclera (S) externally in the foreground view (4). In the mirror view (3-M) showing the internal configuration, one can see the effect of this depression as the retina (R) is now reattached and the tear (T) is closed and flat (compare with (1) above). Note that the tear is properly located on the anterior slope of the invagination. (This same configuration would hold true in the case of a circumferential solid silicone element (not shown), with the sutures placed in general 2mm further apart than the width of a given element, which fully encompass the retinal tear.) (Art from Jaypee Highlights Medical Publisher).



In general, when solid silicone elements are used, sutures are placed 2 mm further apart than the width of a given element. When cylindrical sponges are used, sutures are placed 2 1/2 mm to 3 mm outside the diameter of the sponge. In other quadrants where retinal pathology is not present, the band or the encircling element is placed about 3 mm to 4 mm behind the ora serrata. The scleral buckle is placed loosely to avoid any elevation of intraocular pressure.

Sealing the Retina

The next step involves inducing an adhesive chorioretinal irritation in order to create the scar that will seal the retina. The use of cryotherapy or diathermy has created some controversy in the past. While some reports have suggested that cryotherapy may cause pigment dispersion, which can in theory, lead to PVR, no clinical studies have confirmed this statement. Most problems with this method are caused by overdosing. The surgeons must indent only with the tip of the cryo-probe and not with the shaft to avoid inadvertent posterior freezes. The application of the first freeze to the most anterior aspect of the area of treatment so as to access both location and intensity of cryotherapy, is also recommended.

Some surgeons use diathermy, which requires scleral dissection in order to apply the thermal treatment in a controlled manner and without any scleral damage. It is important to understand that the surgeon's preferred treatment modality will depend upon the type of training he has received.

Under indirect ophthalmoscopic visualization (Figure 6), we prefer the use the cryoprobe to depress the sclera precisely on the area of the retinal tear. With a small break, the cryoprobe should be depressed precisely at the break, and with a large break it should be depressed at the edges. The retinal pathology must be surrounded by cryoapplications. When treating horseshoe tears, the surgeon must reach the ora serrata from either side of the tear to prevent a recurrence of retinal detachment. Treatment should be applied just long enough for the color of the choroid to begin to change to white. Allowing ice crystals to form is an over application of the treatment, which can lead to pigment dispersion.

Laser treatment with argon or a diode laser attached to an indirect ophthalmoscope has become an alternative to cryotherapy or diathermy. The sclera is depressed in the area of the retinal tear, displacing the sub-retinal fluid and at the same time bringing the pigment epithelium in contact with the neuroretina (Figure 14). This facilitates a positive reaction that involves both the pigment epithelium and the retina.

While we use cryotherapy in most cases, others prefer the diode laser for an adequate and more gracious way to treat some retinal tears during primary retinal detachment surgery. Laser is an alternative for treating patients with clear media, where there is good visualization of the retinal tear. Patients with some degree of opacification of the lens (or of the capsule if they are pseudophakic) are better candidates for cryotherapy. A probe for transscleral diode laser application is another modality.



Figure 14: Laser Attached to Indirect Ophthalmoscope Treating and Sealing the Tear. Today there is another alternative to cryotherapy or diathermy: laser treatment with the argon or the diode laser attached to an indirect ophthalmoscope. In this internal/external conceptual view, a section of sclera (S) is shown removed to reveal a cross section during scleral depression (arrow) with an applicator (A) and laser application (L). With corresponding visualization through the indirect ophthalmoscope (O), the scleral invagination is seen in the area of the retinal tear (T). This scleral depression displaces the subretinal fluid and at the same time brings the pigment epithelium in contact with the neuroepithelium during application of the laser (L). This facilitates a good reaction that involves both the pigment epithelium and the retina. Note existing circumferential exoplant (E). (Art from Jaypee Highlights Medical Publisher).

Draining the Subretinal Fluid

After the retina is sealed, the next step is the drainage of the subretinal fluid. This procedure enables the surgeon to decrease the intraocular volume, settle the retinal breaks on the buckle, and obtain a deeper indentation of the sclera to counteract the vitreous traction. Draining of subretinal fluid is recommended in: highly myopic detachments, aphakic and pseudophakic eyes, bullous detachments, multiple breaks, significant vitreous traction, giant tears, inferior breaks, and thin scleras.

The first step in draining the subretinal fluid, using indirect ophthalmoscopic visualization, is to select an area with an adequate amount of fluid to avoid damage to the retina. An area, in which preretinal membranes are present, is preferable because a stiff retina is less likely to be incarcerated. If possible, the surgeon should drain just above or just below the horizontal rectus in order to decrease the risk of bleeding. It is better to drain from the nasal side because, if bleeding occurs, there is less chance the blood will run under the macular area. When subretinal fluid does not reach the horizontal meridians, draining must be done elsewhere; either side of the vertical rectus muscle is another possible site.

Surgical Technique for Sclerotomy

After the drainage site has been chosen, a 3 mm to 4 mm sclerotomy is made with a 64 Beaver blade, under microscopic visualization. The sclera is incised until the choroid is

visualized (Figure 15). Mild cautery applications to the scleral edges cause some gaping of the wound to allow better visualization of the choroid. A mattress 5-0 polyester suture through the right lip of the sclerotomy is placed and gently pulled by the assistant to keep the wound open while the surgeon pulls on the other lip using a 0.3 mm toothed forceps (Figure 16). The illumination and the magnification of the microscope allow the surgeon to avoid the choroidal vessels and to apply exact diathermy touches, using the probe designed for intraocular applications if needed. At this point all external pressure must be avoided.

Then, using a sharp 27 half-inch bent needle, posteriorly oriented to avoid damage to the overlying retina, the surgeon stabs the choroid just enough to enter the subretinal space (Figure 17). The needle is then quickly removed, and the fluid begins to drain (Figure 18). The loss of volume and pressure might be compensated by slightly indenting the eye with cotton tip applicators, which are placed between the globe and the periorbital tissue, away from the drainage site. If the fluid suddenly stops draining, the fundus must again be inspected with the indirect ophthalmoscope before any additional maneuver is attempted. Some pigment granules might be seen in the subretinal fluid

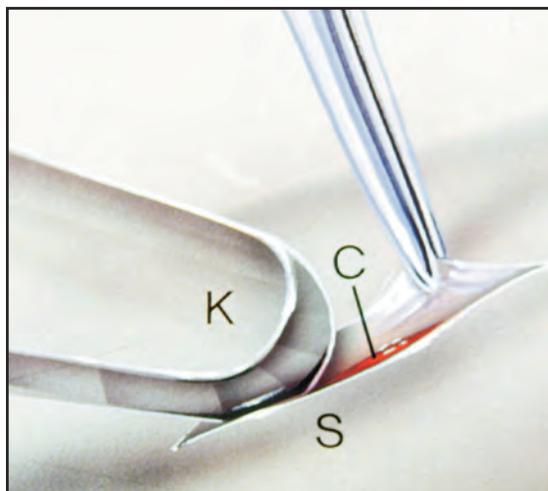


Figure 15: Drainage of Fluid - Surgical Technique for Sclerotomy - Stage 1 - Incision. After the drainage site has been selected, under microscopic visualization, a 3mm to 4mm sclerotomy is made with a 64 Beaver blade (K). The sclera (S) is incised down until the choroid (C) is visualized. (Art from Jaypee Highlights Medical Publisher).

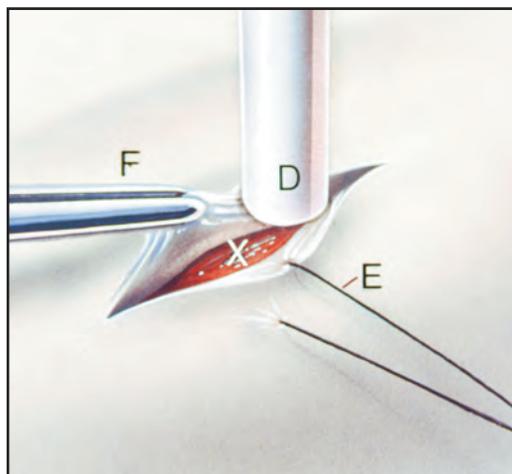


Figure 16: Drainage of Fluid - Surgical Technique for Sclerotomy - Stage 2 - Keeping the Wound Lips Open. Mild cautery (D) is applied to the wound edges to create some gaping of the wound for improved visualization of the choroid. A mattress 5-0 polyester suture (E) is placed through the right lip of the sclerotomy. This suture is gently pulled by the assistant to keep the wound open while the surgeon pulls on the other lip using a 0.3 mm toothed forceps (F). Good choroidal exposure, good illumination and microscope magnification allow adequate visualization by the surgeon to avoid choroidal vessels during diathermy application to the area denoted by the (X) on the choroid. This is the area of the choroid which will be opened. (Art from Jaypee Highlights Medical Publisher).

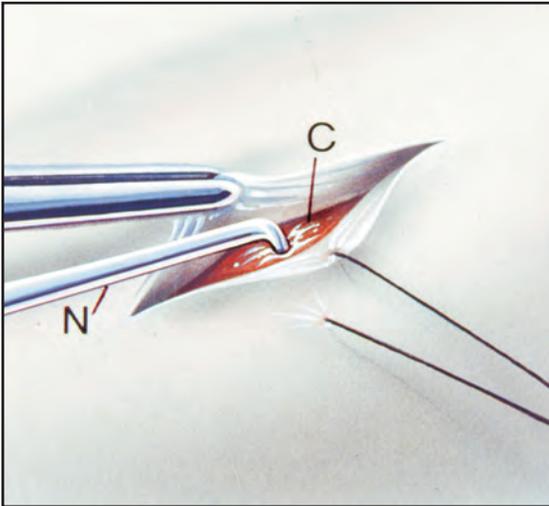


Figure 17: Drainage of Fluid - Surgical Technique for Sclerotomy - Stage 3 - Stabbing the Choroid. Using a sharp 27 half inch bent needle (N), posteriorly oriented to avoid damage to the overlying retina, the surgeon stabs the choroid (C) just enough to enter the subretinal space. The needle is then quickly removed. (Art from Jaypee Highlights Medical Publisher).

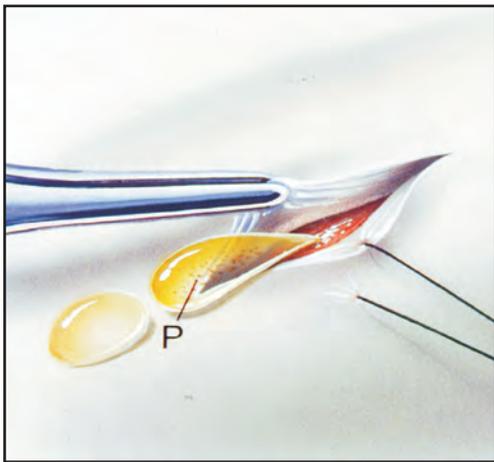


Figure 18: Sclerotomy Technique - Fluid Actually Draining. When the needle is removed, fluid begins to drain as shown. If the fluid ceases to drain, the fundus must be examined with the indirect ophthalmoscope. Some pigment granules (P) may be seen in the subretinal fluid when the drainage is almost complete. (Art from Jaypee Highlights Medical Publisher).

when the drainage is almost complete. The ocular fundus is once again inspected with the indirect ophthalmoscope to evaluate the amount of residual fluid and the position of the tears. It is rarely necessary to drain all subretinal fluid, as long as the buckle is adequate in size and position.

Closing the Scleral Wound

The scleral wound is prepared with a pre-placed suture, which prevents certain types of complications (Figure 19). The scleral buckle sutures are then tightened, beginning at the area of the breaks, and moving to the other quadrants. If the eye is too soft, filtered air is injected through the pars plana to restore its volume. An air bubble, or a mixture of air and a perfluor-carbonated gas, also helps to flatten the retina if a fish mouth effect to the retinal tear is present. This fish mouth type of gaping can be induced by relative circumferential shortening of the retina, which causes radial retinal folds to form over the buckle. The suture ends are adjusted enough to obtain the desired indentation effect to close the tears. They are secured with a silicon sleeve, a tantalium clip, or a non-absorbable suture. When a 4 mm cylindrical sponge is used, a 5-0 polyester suture will secure it from end to end. The fundus is re-examined to evaluate the scleral indentation and the position of the breaks as well as to assure optic nerve perfusion (Figure 20). Tenon's capsule is secured to the sclera next to the insertion of the rectus muscles in each quadrant to prevent any future extrusion of the explant. If the explant is not

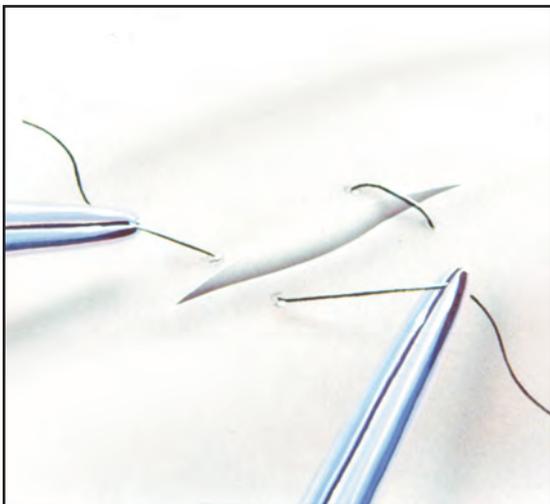


Figure 19: Sclerotomy Technique - Final Stage - Closing the Wound. The wound is closed with the pre-placed suture as shown. The scleral buckle is tightened. (Art from Jaypee Highlights Medical Publisher).

totally covered with Tenon's capsule, the risk of subsequent erosion and extrusion of the exopant is increased.

After Tenon's layer is closed satisfactorily, the conjunctiva is pulled anteriorly, and the radial cuts are closed with polyglycolic acid sutures, an antibiotic and a corticosteroid are applied topically.

Anatomical and Visual Result after Scleral Buckling

The overall rate of anatomical reattachment with current techniques is 90%. Aphakic and pseudophakic eyes have a slightly less favorable prognosis. Whether the macula was detached and for how long is the primary

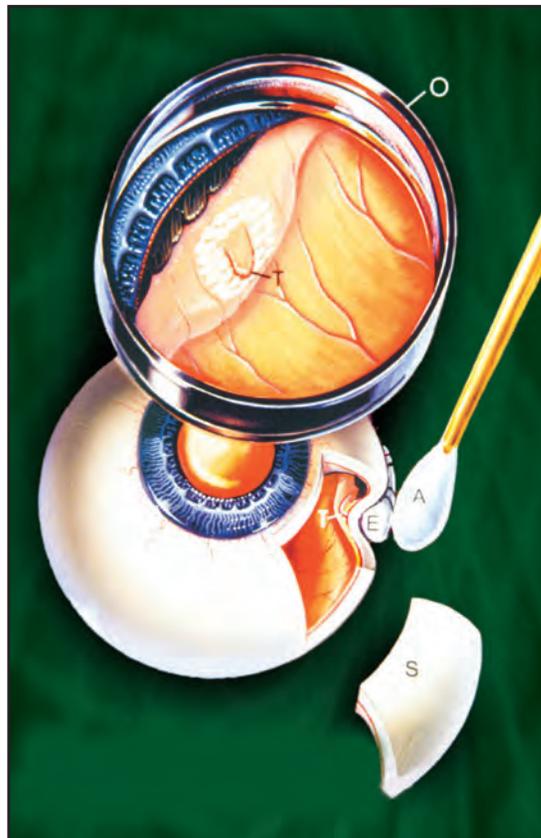


Figure 20: Final View of Buckle with Retinal Indentation and Sealing. This internal/external conceptual illustration shows a cross section and corresponding surgeon's view of the final configuration of a circumferentially placed sponge exopant (E). The cross section shows a portion of sclera (S) removed for clarity. The surgeon's view is through the indirect ophthalmoscope (O). Note the indented configuration in both views. The retina is reattached and the tear (T) is flat. Also note that the tear is properly positioned on the anterior slope of the invagination. (Art from Jaypee Highlights Medical Publisher).



pre-surgery determinant of post-operative visual acuity. While 87% of eyes with retinal detachment sparing the macula recover visual acuity of 20/25 or better, in eyes with successful reattachment of macula-off detachment, approximately 40% to 60% of eyes have final visual acuity of 20/50 or better.

PNEUMATIC RETINOPEXY

Pneumatic retinopexy, first introduced by Dominguez in Spain and then by Hilton in the U.S., allows the reattachment of the retina by the intravitreal injection of an expanding gas bubble. Transconjunctival cryopexy or laser photocoagulation as well as post-operative head positioning are mandatory for an increased rate of success. Pneumatic retinopexy can be performed in an office setting and may be the most cost-effective means of retinal reattachment.

Indications

Pneumatic retinopexy is an alternative for the treatment of retinal detachments in cases of a single retinal break, or a group of breaks confined to the superior two thirds of the retinal periphery. If the peripheral retinal view is adequate, pseudophakic detachments can also be managed with this technique.

Despite its advantages, some contraindications to this procedure have been identified: (1) in breaks larger than one clock-hour, or

where there are multiple breaks extending more than three clock hours, (2) breaks are located in the inferior four clock-hours of the eye, (3) where there is significant traction on the retinal tears, (4) in cases of patients who are unable to maintain bodily adequate position, (5) due to the brief elevation of the intraocular pressure, advanced glaucoma patients are at higher risk for further optic nerve deterioration, (6) in the presence of cloudy media which prevent correct identification and treatment of the breaks.

Advantages and Disadvantages

Advantages to this technique include: somewhat shorter time in surgery, less inflammation, and less cost to the patient. General anesthesia is not required. However, this technique is not free of complications: (1) high intraocular pressure may develop while introducing the gas into the intraocular cavity. (2) When a gas-bubble has been introduced, there may be pulling on the vitreous and the retina which may result in bleeding or in the development of a new retinal tear. (3) subretinal fluid may shift to the macular area while the bubble is pushing the break and the retina. This fluid behind the fovea will worsen the prognosis.

As a consequence, it is very important to carefully select the patient on whom we decide to apply pneumatic retinopexy.



Surgical Technique

Preparing the Syringe with Gas

Sulfur hexafluoride (SF_6) and perfluoropropane (C_3F_8) are the most frequently used gases. The type and amount of gas depends on the number and location of the breaks. A 0.3 mL gas-bubble covers more than 45° of the area of the retina, but it takes approximately a 1.2 mL bubble to cover an arc 80° to 90° of the surface area. A dose of 0.5 mL of SF_6 doubles its size in 36 hours, and 0.3 mL of C_3F_8 quadruples it in the same period of time. In most cases a gas bubble volume of 1 mL, which requires an injection of 0.5 mL of pure SF_6 , would be enough. The injected gas bubble before expansion must be moderately larger than the retinal break, to prevent subretinal gas. The area of the breaks should be covered by the bubble for at least 5 days. Air can be used but requires a larger volume and sometimes its longevity might be insufficient to allow a chorioretinal scar to form.

Frequently a three (3) cc syringe with a millipore filter is used to draw the gas from a low-pressure system connected to the SF_6 tank (the tube connecting the gas cylinder with the syringe, including the filter, is flushed through with gas to ensure no dilution with room air). A disposable 30 gauge needle is then placed tightly on the syringe, and the excess gas is expelled leaving the exact amount intended for injection. This amount may

vary depending on the size and location of the breaks. This gas lasts about two weeks inside the eye (0.3 mL of C_3F_8 last about 38 days).

Patient Preparation

The pupil is dilated in the usual manner using cyclopentolate 1% and neosynephrine 2.5%. A preoperative softening of the eye is recommended; for this purpose, personally, we prefer to apply a "Mercury Bag" which is placed over the eye for 20 to 30 minutes, prior to the injection. Then topical and subconjunctival anesthesia is given.

Retinopexy

Initially some surgeons delayed cryopexy (or laser treatment, applying a conventional laser through the pupil and through the gas-bubble, or using a diode laser through the sclera, instead), until the retina has been flattened against the retinal pigment epithelium. The technique has evolved into a one stage operation; cryotherapy may be applied to detached retinal break(s), if they are not highly elevated prior to the gas injection. It is often possible to apply laser treatment through a large gas bubble, or the bubble is moved away by tilting the head of the patient. The laser indirect ophthalmoscope allows treatment of the extreme anterior periphery, and, if the detachment is shallow, it may be possible to apply a laser using scleral depression to flatten the retina.

Gas Injection into the Eye

Sterilization of the ocular surface is obtained with topical povidine iodine solution. After placing a sterile lid speculum and with the patient supine, the head and the eye are turned approximately 45° to one side so as to place the pars plana uppermost. The injection is usually performed temporally, 4 mm behind the limbus, unless the pars plana is detached or large retinal breaks are present in that area, in which case another site is selected. In a patient with retinal detachment in whom there is intraocular fluid the gas is placed under the anterior hyaloid. The needle is directed toward the center of the vitreous and inserted to a depth of 7 to 8 mm and then is partially withdrawn, so that about 3 mm of the needle is left inside the eye. In order to create a single gas-bubble, the gas should be injected in a moderately brisk fashion, avoiding the formation of so-called "fish eggs", in which multiple small bubbles at the needle tip are formed. As the needle is withdrawn from the eye, a sterile cotton tip applicator is rolled over the needle-tract and the head of the patient is rotated to the opposite side to prevent leakage of the gas. Immediately following this, an indirect ophthalmoscopy is performed to corroborate the patency of the central retinal artery. If the artery is closed and does not reopen within 10 minutes a paracentesis is done to lower intraocular pressure. Finally antibiotic-steroid drops, or in ointment, are applied, and the eye is patched.

In patients with a bullous retinal detachment which extends almost to an attached macula, placement of a gas bubble might push fluid into the macula and detach it. To prevent this problem, after the injection, the head of the patient is turned to a face-down position; over a period of 10 to 15 minutes the patient's head is very gradually rotated until the retinal break is uppermost, causing the bubble to roll toward the retinal break, pushing the subretinal fluid away from the macula and back into the vitreous, and flattening the retina.

Positioning of the Patient

Great effort must be made to ensure that the patient and his/her family understand the importance of proper positioning, so that the retinal break is uppermost. It may be helpful to draw an arrow on the patient's eye-patch, or on their forehead, to indicate the meridian of the tear, so as to help in postoperative positioning. The patient is instructed to point the arrow toward the ceiling. In order to avoid cataract formation, the patient has to avoid lying on the back, facing towards the ceiling. As an example, if we have a tear in the nasal superior quadrant of the right eye, we would keep the head tilted toward his/her right side so that the bubble migrates to the superior nasal quadrant. If the tear is on the superior temporal quadrant of the right eye, the tilting is done toward the left side. The correct head position should be maintained during the waking hours for at least five days.



Remaining in this position during sleep is advisable. The contact of the air-bubble with the edges of the tear blocks the passing of fluid to the subretinal space. Because of this tamponade effect the subretinal fluid will be absorbed within approximately 24 hours. If the retinopexy has not been previously applied, cryo, or laser treatment, is applied to the edges of the tear to create a chorioretinal adhesion and thus seal the tear.

The patient should be seen at frequent intervals during the early postoperative period to assess adequacy of the retinopexy, and to rule out possible complications, including new or missed retinal breaks and recurrent retinal detachments.

Complications

Intraoperative Complications

The most common intraoperative complication is the unwanted injection of the gas anterior into the anterior hyaloid phase, which gives the appearance of a "sausage", to the injected bubble. As the gas expands over 24-48 hours, it usually breaks through the anterior hyaloid face and enters the vitreous cavity (this complication is avoided by injecting deeper into the center of the vitreous cavity, which ensures penetration of the anterior hyaloid face).

Another intraoperative complication is the formation of subretinal gas when small gas bubbles gain access to the subretinal space.

After placing the patient in the supine position and with scleral depression the bubble is relocated. The formation of new retinal breaks has been reported in 14% to 19% of cases (Figure 21).

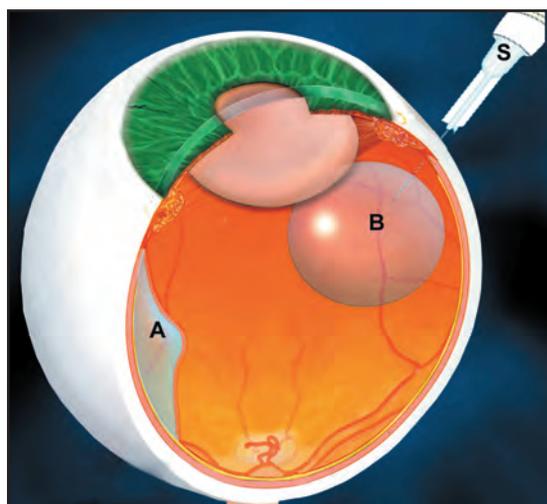


Figure 21: Complications during Pneumatic Retinopexy. A common complication is injection of gas into the anterior hyaloid space or even subretinal, which gives an appearance of a "sausage" to the bubble injected (A). This complication will cause a re-detachment of the retina. This side view illustration focuses the proper maneuver to inject the bubble into the vitreal space (B) avoiding the retina with the needle (S). (Art from Jaypee Highlights Medical Publisher).

Postoperative Complications

Cataract formation, endophthalmitis and extension of the retinal detachment can occur. Formation of new breaks, PVR and a reopening of retinal breaks have also been described.

Anatomical and Visual Results

With one operation, and with occasional postoperative cryotherapy or laser supplementation, retinal reattachment has been achieved in 80% to 84%. In cases of failure, a subsequent scleral buckling can be offered which would increase the success rate of retina reattachment to 98%. The visual acuity recovery has been reported to be statistically significantly better in patients after pneumatic retinopexy, particularly if the detachment included the macula for at least 2 weeks, when compared to a scleral buckle.

LINCOFF'S ORBITAL BALLOON

What is a Lincoff Balloon and How does it Work?

The Lincoff's balloon is a non-drainage technique and is another alternative used to create a temporal buckling effect. It was

described by Harvey Lincoff, M.D., in New York, in 1979. This technique consists of the use of a small balloon made of siliconized latex, - which combines the tissue inertness of silicone with the strength and elasticity of latex-, at the end of a soft plastic tube which has been modified by the addition of a steel stylette that stiffens it, facilitating insertion. A balloon catheter that accepts a fiberoptic stylette, in order to facilitate location, has been developed. The proximal end of the catheter accepts the steel or fiber optic stylette and a plastic-adapter, which has a self-sealing valve for inflation. The balloon is inflated by inserting a 1mL syringe into the plastic-adapter and injecting sterile water. The catheter and balloon are introduced in the subconjunctival space to create a temporary buckling effect and to seal the breaks; the subretinal fluid it absorbs through the retinal pigment epithelium.

Indications

The balloon procedure is suitable for retinal detachments caused by tears that are located within a one-clock-hour arc or 6 mm at the equator. Its use is limited in cases of very posterior tears, and in those with an associated PVR. The extent of the detachment is not a factor for patient selection. A retinal break located beneath a rectus muscle is especially suited for this procedure, whereas a sponge explant placed beneath a muscle, particularly a vertical one, will often cause postoperative diplopia.



Surgical Technique

This surgical procedure is not considered a major surgery and, if needed, it can be done in an office-setting. The procedure is performed with retrobulbar, subconjunctival or topical anesthesia. Accurate transconjunctival localization of the breaks is performed and a mark with ink is placed on the conjunctiva. A second mark is made more anteriorly in the exact meridian of the tear, a little posterior to the limbus (where the conjunctiva and Tenon's capsule merge). Transconjunctival cryopexy is then applied to treat all retinal breaks. Alternatively laser can be applied at a later time when the retina is attached. A sterile field is then prepared applying 10% povidone iodine solution to the conjunctiva. A 2 mm incision is made through conjunctiva and Tenon's capsule at the anterior mark. The deflated balloon is inserted into Tenon's space and subsequently advanced to the location of the break. The stylette is then withdrawn; the balloon is inflated with 0.5 mL of sterile water, and its position is checked with an ophthalmoscope. If necessary, the location of the balloon can be adjusted so that it lies directly beneath the break. Then the balloon is inflated under ophthalmoscopic control to a volume appropriate to the height and width of the break. This usually requires an additional 0.75 to 1.0 mL of water. The sudden expansion of the balloon causes a temporary rise in intraocular pressure, making it necessary to check the patency of the central retinal artery; if required, water from the balloon is withdrawn until flow is restored. To observe the process within the eye one

may use indirect ophthalmoscopy, or the wide angle contact lenses, which allow the surgeon to inspect the periphery and the buckling effect in the specific area of the tear. The main wide angle lenses are the Stanley Chang lens and the Schlaegel Panfunduscope lens (Figure 22) as advocated by E. Malbran. The external portion of the catheter and the valve are taped to the patient's forehead, antibiotic ointment is applied, the lid is closed over the tube, and the eye is then patched. The fellow-eye is also patched overnight.

The eye is checked on the first-postoperative day. If needed, the balloon can be enlarged by injecting additional water. After 7 days, the balloon is completely deflated and withdrawn under topical anesthesia. No conjunctival suture is needed.

Results

Successful reattachment of the retina with this technique has been reported in 64% to 96% of cases. Visual results are similar to those achieved with scleral buckling. A disadvantage is the limited number of cases in which its use is appropriate. The indications for the orbital balloon are very similar to pneumatic retinopexy; however the latter is a more popular procedure.

Although this technique is clearly of value in selected cases, it has not gained widespread popularity in the United States, and it probably is not employed as frequently at this time, as it was in the past.

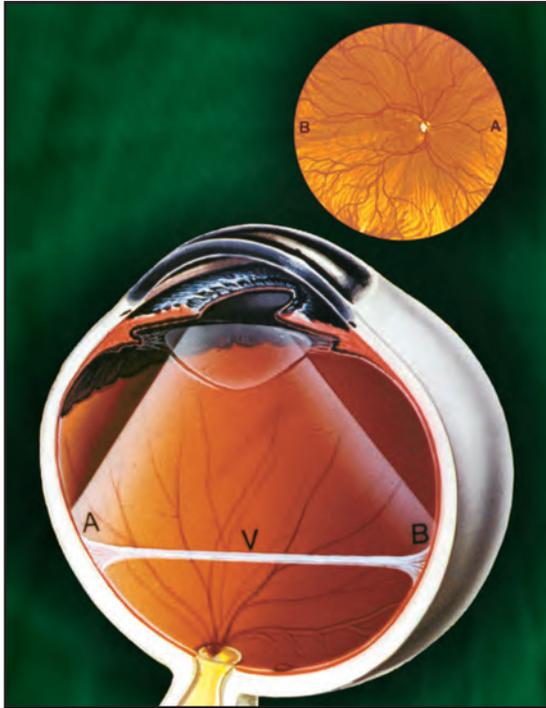


Figure 22: Panoramic Image of Vitreo-Retinal Cavity with Wide Angle Contact Lenses (Panfunduscope) The panfunduscope provides the surgeon with a much wider field of view (V) to better appreciate panoramic intravitreal and retinal tissue relationships. As an example, the entire structure of the vitreous band spanning from A to B can be seen in a single view, thus providing the surgeon with a most accurate and all-encompassing display of the intravitreal pathology. Such all-encompassing information available to the surgeon can determine the very best approach to solving a problem. The inset shows the resultant field of view of the fundus seen by the surgeon. (Art from Jaypee Highlights Medical Publisher).

Complications

Because the procedure is entirely extraocular, complications are rare. A postoperative shift in the position of the balloon may allow the break to remain open. Also spontaneous deflation of the balloon has been described.

PRIMARY VITRECTOMY AND FLUID-GAS EXCHANGE

Pars plana vitrectomy combined or not with scleral buckle, and fluid-gas exchange, is becoming the more popular approach as an initial surgical therapy for rhegmatogenous retinal detachment. In these cases, vitrectomy is selected to decrease the difficulties and risks associated with scleral buckling, to help relieve vitreoretinal traction in cases of moderate-severe PVR. The pars plana vitrectomy is the most invasive approach of all the techniques described above, and may cause postoperative complications, such as new retinal breaks and detachments, and it promotes a high incidence of cataract formation; therefore today this procedure is mainly considered in aphakic or pseudophakic eyes.

Surgical Technique

The surgical technique consists in performing a pars plana vitrectomy. After core

vitrectomy, emphasis is placed on removing vitreous adherent to the margin of the retinal breaks. Sometimes the traction is best removed by excising the flap of a horseshoe tear (Figure 23). In order to stabilize the retina, after the posterior vitreous has been completely removed (with previous separation of the posterior hyaloid), heavy fluid can be used (i.e. perfluorocarbon liquid). Once the vitrectomy has been completed, additional heavy fluid is injected to flatten the retina. The subretinal fluid will be pushed through the retinal break, exhibiting a schlieren sign, seen when two liquids of differing refractive index are mixed; this may help to rule out any coexistent peripheral retinal breaks that were not seen preoperatively (Figure 24). When the heavy fluid is near the posterior edge of the tears, an extrusion cannula is placed in the break and a total fluid-gas exchange is performed, which reattaches the retina. Finally the fluid posteriorly located in front of the retina is extruded. Alternatives for draining the subretinal fluid are: the passage of an extendable silicon extrusion catheter through a retinal break, transscleral drainage or making a posterior or anterior retinotomy. Once the retina is flat, retinal breaks are treated with endolaser photocoagulation or external cryopexy (Figure 25).

Results

The results of four reports of this technique yield a weighted average of 78% single-operation success and 89% ultimate anatomic success with one or more operations. These results

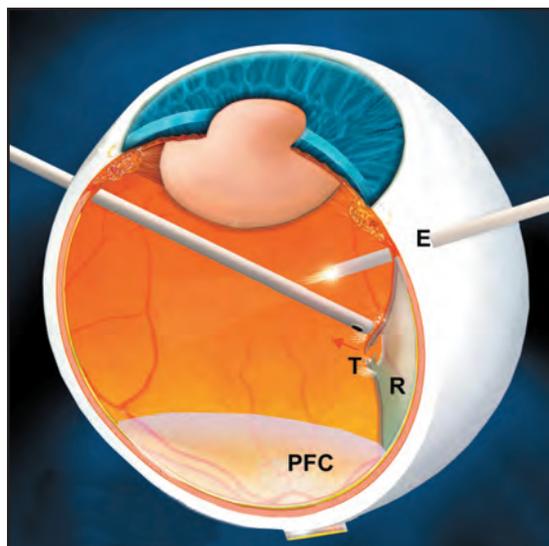


Figure 23: Primary Vitrectomy. During this process it is important to remove the vitreous adherent to the margin of the retinal tear and detachment (R). The vitreal traction may be removed by excising the border of the flap of the retinal tear (T). The injection of perfluorocarbon liquid may be useful to retain the retina attached during the vitrectomy (PFC). Endoillumination (E). (Art from Jaypee Highlights Medical Publisher).

appear to be inferior to those expected from other techniques for primary uncomplicated retinal detachments. In general the preliminary results of the vitrectomy procedure are comparable to those of pneumatic retinopexy, and this is consistent with the fact that both techniques work by a similar mechanism. However, there appears to be little apparent advantage of vitrectomy and intraocular gas injection over pneumatic retinopexy for cases

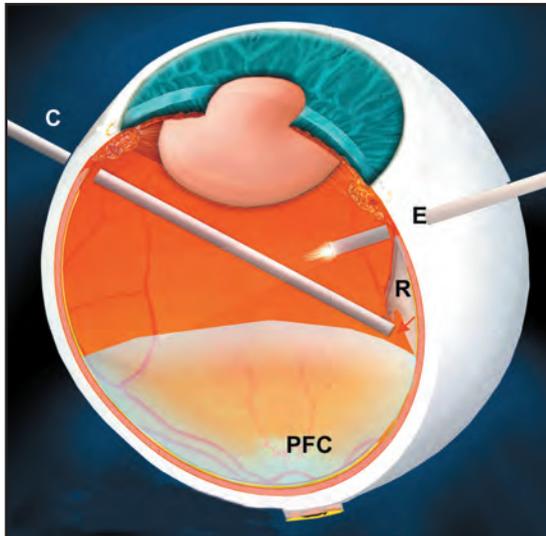


Figure 24: Sub-Retinal Fluid Drainage Process. When the perfluorocarbon liquid (PFC) is near the posterior edge of the causative retinal tear (R), an extrusion cannula is placed in the break and a total sub-retinal fluid drainage is initiated to reattaches the retina (arrow): Once the vitrectomy is performed a fluid-gas exchange procedure is performed by visualization with endoillumination in one hand (E) and the extrusion cannula in the other (C). (Art from Jaypee Highlights Medical Publisher).

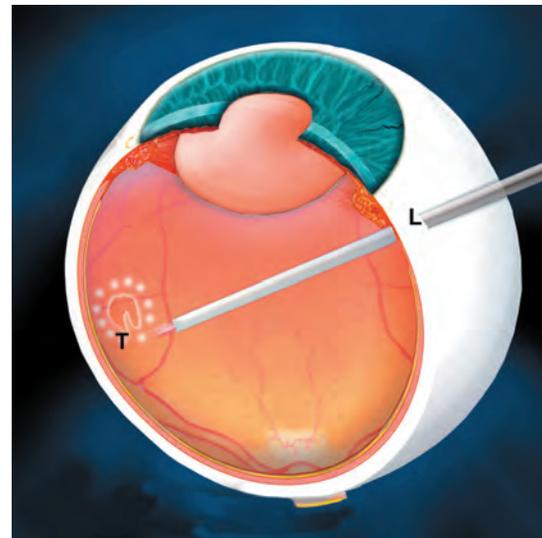


Figure 25: Endophotocoagulation. At the end of the process, once the retina is flat, all retinal tears or lesions are treated with endolaser photocoagulation (T). In selected cases the surgeon may use external cryopexy as a viable option. In this phase we may observe how the retinal tears is sealed with several rounds of endolaser application (L). (Art from Jaypee Highlights Medical Publisher).

in which the latter technique can be used. It is useful in cases which are not favorable to simpler procedures, however, the surgeon must take into consideration, before choosing one surgical technique over the other, the particular conditions of the patient, such as age, lens status, retinal and vitreal pathology.

SCLERAL BUCKLE VERSUS PRIMARY VITRECTOMY

A recent study by Heimann et al, showed a benefit of the scleral buckle over the primary vitrectomy as a primary treatment for rhegmatogenous retinal detachment in phakic eyes with respect to the best corrected visual



acuity. No difference in the visual acuity was demonstrated in the pseudophakic trials; based on a better anatomical outcome. On the other hand, pars plana vitrectomy was recommended in this particular group of patients.

VITREOUS SUBSTITUTES

Vitreous substitutes have been used to facilitate retinal reattachment surgery since the last century. The first (one ever used) was air in 1911, which provided adequate retinal tamponade. Nonetheless, air tends to be absorbed rapidly from the vitreous cavity diffusing across the retina, limiting its tamponade effect. The use of perfluorocarbon gases began in the 1980s. These gases remain in the vitreous long enough to produce an effective tamponade; however, this prolonged persistence in the eye, may also come with the development of complications such as an increase in intraocular pressure and lens opacification.

In the recent decades, great advances have been made in the development of fluids, such as collagen and hyaluronic acid, gases, silicone oils, perfluorocarbon liquids and polymer hydrogels, that can be used intravitreally to facilitate the surgery of retinal reattachment.

USE OF INTRAOCULAR GASES

Gases Mostly Used and When

In retinal detachment surgery an intraocular gas-bubble is frequently used to flatten the retina by providing a temporary internal tamponade. The development of gases that provide longer internal tamponade has improved the ability to successfully manage complex retinal detachments. They are also used for pneumatic retinopexy in selected conventional rhegmatogenous retinal detachments, and for the treatment of macular holes. Two expanding gases, sulfur hexafluoride (SF_6), and perfluoropropane (C_3F_8), are the most commonly used.

Use of SF_6

SF_6 is a colorless, odorless, chemically inert and nontoxic gas, which expands twice its volume in 24 to 48 hours. Its longevity inside the eye is from 10 to 12 days. SF_6 gas is commonly used in PR. If the bubble is larger than the retinal break, the surface tension of the gas prevents it from passing through the hole.

SF_6 is commonly used in vitreoretinal surgery, such as retinal detachment and proliferative diabetic retinopathy. The effect of the gas bubble on smoothing retinal folds and flattening fish mouth tears is only required for a short period. Air is preferable in situations in which the volume of gas is adequate to tamponade the break. SF_6 should be considered when the expansion properties of a gas are desirable to achieve a larger volume, which will tamponade a larger break or multiple breaks. A frequent use of SF_6 is in the management of macular holes, in which vitrectomy is done to remove the posterior hyaloid from the surface of the retina in the macular area, and a mixture of 20% gas and 80% air is introduced to create a tamponade effect and re-attach the edges of the hole (Figure 26). This procedure, if successful, leads to improvement of vision in a significant number of patients.

Use of C_3F_8

C_3F_8 is also inert, colorless, and odorless, is inflammable, and expands four times its volume. Depending of the volume injected inside the eye, it lasts about fifty five days.

The most common situation in which C_3F_8 is used is in rheumatogenous retinal detachment with severe PVR, and severe diabetic retinopathy, where the surgeon peels vitreoretinal membranes, and re-attaches the retina after making a fluid-gas exchange. C_3F_8 is the gas mostly used in PVR surgery. Its use allows the neuroretina to be in contact with the retina pigment epithelium for about 10-15 days with a complete tamponade effect. This

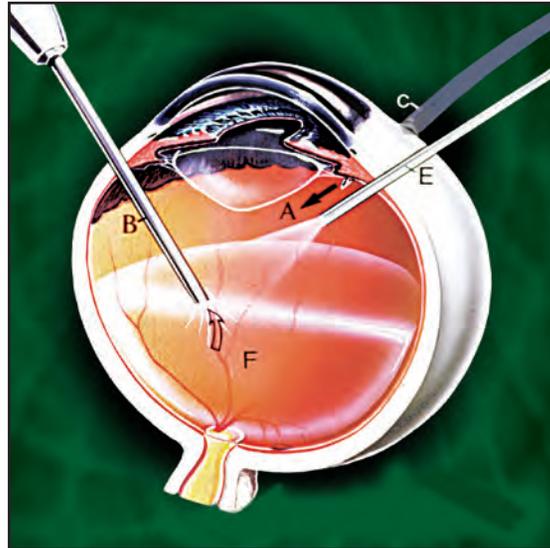


Figure 26: Mechanism of Fluid-Gas Exchange to Reattach the Retina Following Vitrectomy, Relief of Traction and Tamponade Effect in Macular Holes. Fluid-gas exchange is performed following vitreoretinal surgery to maintain the retina attached to the pigment epithelium. First, the intraocular fluid is exchanged with air, until air (A) fills 100% of the cavity as shown. The air is introduced into the vitreoretinal cavity by an air pump via an infusion cannula (C) placed in the inferior temporal quadrant. At the same time, fluid (F) is aspirated via an aspiration cannula (B) placed in the superior nasal quadrant. Next, the air is exchanged with a mixture of gas and air (20% gas with 80% air if SF_6 is used and 15% gas with 85% air if C_3F_8 is used). A light probe (E) for endoillumination is present in the superior temporal quadrant during this exchange. (Art from Jaypee Highlights Medical Publisher).



makes possible a stable chorioretinal adhesion from either laser or cryotherapy. C_3F_8 may also be used in cases of iatrogenic retinal breaks while removing or delaminating the membranes. When this complication arises, the use of gases makes the final results much more satisfactory.

These gases, SF_6 and C_3F_8 are used industrially. Consequently, they are available in most countries. It is important to request medical grade, and to filter them before use.

Fluid Gas Exchange for Gas Injection

After performing vitreoretinal surgery to flatten the retina, a fluid-gas exchange is frequently done. Air is introduced into the vitreoretinal cavity through the infusion cannula, by an air pump usually integrated in the vitrectomy machine. Fluid is drained from the same cavity, and from the subretinal space, through an extrusion cannula. At the same time that the fluid is being extruded through the cannula, air is being introduced by the air pump, filling the vitreoretinal cavity until it occupies 100% of its space.

The air-gas exchange is done by insufflating an air-gas mixture with a concentration of 15% C_3F_8 or 20% SF_6 . This is achieved by disconnecting the air pump through which air is going into the eye and connecting a 20 cc syringe with the known air-gas mixture to the infusion cannula (Figure 27). To obtain the 15% con-

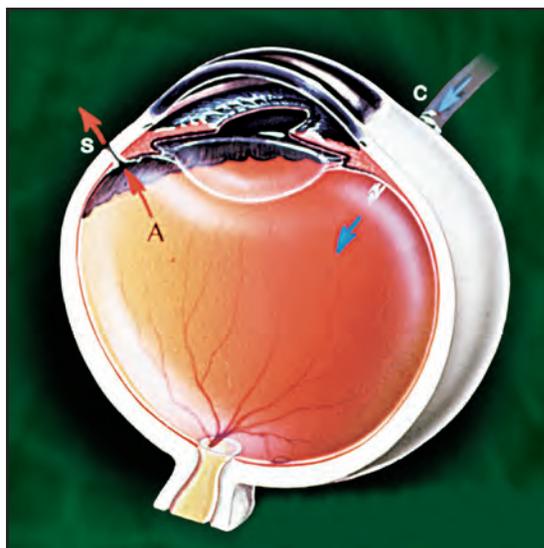


Figure 27: Mechanism of Air-Gas Exchange to Leave an Intraocular Mixture of Gas and Air. The gas mixture is introduced (blue arrows) via the infusion cannula (C) as the air (A) exits (red arrows) the eye via the open sclerotomy (S). (Art from Jaypee Highlights Medical Publisher).

centration of C_3F_8 in the air-gas mixture, one should aspirate 3 cc of pure C_3F_8 into a 20 cc syringe; then air is aspirated until the 20 cc are completed. A concentration of 20% SF_6 and 80% air is prepared by aspirating 4 cc of SF_6 followed by 16 cc of air.

Another alternative, after the eye has been left insufflated with air (instead of fluid), is to wash the air from inside the eye by injecting the prepared concentrations of gas through one of the already closed sclerotomies, connecting a millipore filter and a 30-gauge needle to the syringe, and allowing



the excess gas to be extruded through another needle connected to a small syringe, with the plunger removed, and introduced through the opposite closed sclerotomy.

The Use of Intraocular Gases vs Silicone Oil in Rhegmatogenous Retinal Detachment

Comparative Effectiveness

In the United States, a multicenter control trial was made to evaluate the effectiveness of silicone oil in comparison to the C_3F_8 or SF_6 gases, in cases of PVR. The study concluded that there was no difference in results in attaining a permanent reattachment of the retina.

In general, the tamponade elected in a particular case depends on the experience and preference of the surgeon. In a retinal detachment due to a large giant tear, we now prefer the use silicone oil as the tamponade.

Problems With Silicone Oil

The problem with using silicone oil is that we have to perform a second surgical procedure to withdraw this substance. This needs to be done about three to six months after the initial surgery, when the retina is re-attached and stable from the tamponade

effect. Furthermore, silicone oil left in the vitreous cavity for long periods of time (over six months) may lead to sight-threatening complications such as keratopathy, glaucoma and cataracts. In cases of inferior retinal detachment due to inferior breaks, silicon oil may not be the best option; due to its low density that may result in limited or reduced inferior tamponade. Another issue is that silicone oil may stimulate a peri-silicone proliferation of scar tissue. These are the main reasons why many retinal surgeons do not like to use silicone in most of their cases.

Indications for Silicone Oil

Silicone oil is particularly indicated in patients who live at higher altitude than the surgical center where the surgery takes place and/or patient who need to travel by plane soon after the procedure. Rapid decompression of atmospheric pressure during air travel may cause an elevation of intraocular pressure in patients with a large intraocular gas bubble. This rise in pressure may compromise blood flow through the central retinal artery. Lincoff et al. support the indications from clinical experience, that volumes of intraocular gas up to 1.0 mL can be tolerated. Silicone oil allows the patient to travel by plane after a successful retinal surgery. When vitreoretinal traction has not been relieved or when it can be anticipated that it will recur, the use of silicone oil may be valuable. Clinical experience has prompted the restriction of silicone-oil tamponade to severe cases of retinal detachment, selected patients with complex diabetic retinopathy, viral retinitis,



and severe trauma. It seems that in eyes with severe anterior PVR and clinically significant posterior PVR changes, a better visual prognosis has been attained when silicone oil has been used. Some concerns about the long-term effect of silicone oil on the retina and other tissues, have been expressed.

PERFLUOROCARBON LIQUIDS (PFCLs)

They represent a significant development in vitreoretinal surgery. Dr. Refojo in Boston, and Dr. Stanley Chang in New York, were the pioneers in their use. They observed that their weight, their superior tamponade-effect, and their very different refractive-index from water, also made them easily distinguishable from saline solution. Presently, the perfluorocarbon liquids (PFCLs) are used to re-attach the retina in PVR cases, when one have to see the retinal-traction and membranes intra-operatively, and in giant retinal tears, where the posterior edge of the tear is often rolled towards the vitreous cavity. When heavy liquids are introduced after vitrectomy has been performed, the retina is re-attached and the tear is again in contact with the pigment epithelium.

Another use of PFCLs is in the management of crystalline lenses and intraocular lenses traumatically luxated into the vitreous (Figures 28A and 28B), in the management of retinal detachments caused by ocular trauma.



Figure 28 A: Use of Perfluorocarbon Liquid for Dislocated Lens - Stage 1. In cases of removal of a hard dislocated lens, perfluorocarbon liquid (P) can be placed in the eye. Lens fragments float on top of the liquid at a safe distance from the retina. Here a large lens piece (L) is cracked and aspirated with the phaco tip (A) and manipulated with a tissue manipulator (cannula with endoilluminator (E)). Infusion cannula (I). (Art from Jaypee Highlights Medical Publisher).

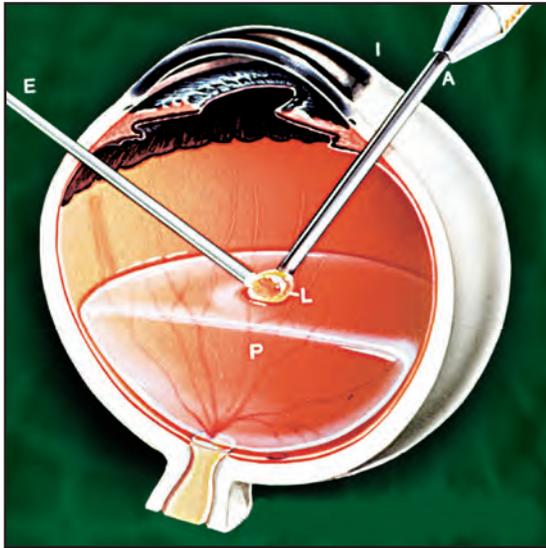


Figure 28 B: Use of Perfluorocarbon Liquid for Dislocated Lens - Stage 2. The last lens piece (L) is shown being aspirated from the eye with the phaco tip (A) as it floats on the perfluorocarbon liquid (P). Tissue manipulator (cannula with endoilluminator (E)). Infusion cannula (I). (Art from Jaypee Highlights Medical Publisher).

Some cases of uncomplicated rhegmatogenous retinal detachments arising from occult retinal break(s), may be treated by vitrectomy and PFCLs, rather than by a scleral buckle alone. PFCLs can help to identify the location of occult breaks by exerting a posterior flattening force that displaces the subretinal fluid through the peripheral break, exhibiting a schlieren sign, seen when two liquids of different refractive-index are mixed. The retinal break(s) can be located by observing the direction of schlieren flow. PFCLs may also produce a very effective tamponade in cases of inferior retinal breaks, when the use of silicone oil may be limited; however, some authors have found irreversible damage to the retina after prolonged periods during which PFCLs remains in the vitreous cavity.

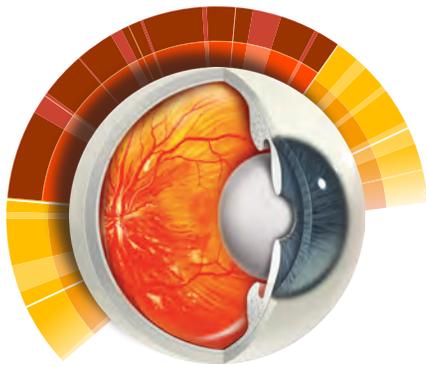
In recent years, the development of second and third generations of heavy tamponade agents, which combine silicone oils and heavy liquids, such as Oxane HD (Bausch and Lomb, Toulouse, France), Densiron 68 (Fluoron Co, Neu-Ulm, Germany), and HWS 46-3000, have shown, at least in preliminary results, better tolerance and tremendous potential in repairing complex retinal detachments.

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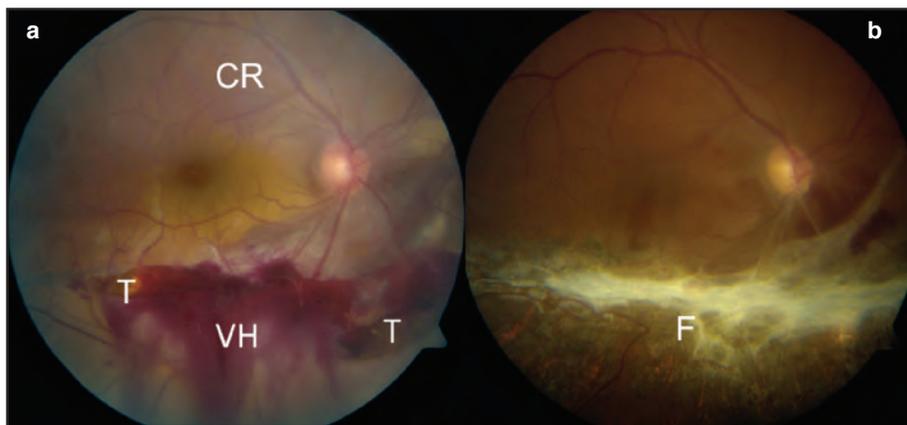
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Management of Giant Retinal Tears

SACHIN MEHTA, MD;
FRANCO M. RECCHIA, MD;
PAUL STERNBERG, JR., MD.

Giant retinal tears are not as prevalent as many other types of retinal detachments. However, they are an important subject because they have traditionally been difficult to repair and have been associated with a lower success rate and more complications than other retinal detachments. While any patient can develop a giant retinal tear spontaneously or

after cataract surgery, several types of patients seem more prone than others to developing giant retinal tears. These include patients with hereditary vitreoretinal abnormalities such as Stickler syndrome.¹⁻³ Giant retinal tears are also associated with trauma in approximately 20% of cases⁴ (Figures 1a and 1b).



Figures 1a and 1b: Traumatic Giant Retinal Tear – Pre-op and 6 Weeks Post-op. **a)** The patient depicted above sustained blunt trauma to the right eye and developed a posterior giant retinal tear (T) extending clockwise from 3 o'clock to 8 o'clock. Visual acuity was 20/200. Note the associated vitreous hemorrhage (VH) and diffuse commotio retinae (CR). **b)** The patient underwent immediate scleral buckling and pars plana vitrectomy with the use of perfluoron, endolaser, and perfluoropropane gas tamponade. 6 weeks postoperatively, the retina remained flat despite the development of extensive subretinal fibrosis (F). Visual acuity improved to 20/80. (Images courtesy of Franco M. Recchia, MD.)



Definition

Giant retinal tears are defined as retinal breaks greater than 90 degrees in extent or circumference. Giant tears are distinguished from other retinal breaks by their size and by the fact that the vitreous gel is attached only to the anterior flap. While a large retinal dialysis can also be considered a retinal tear, the pathogenesis of the two conditions is completely different (Figure 2).

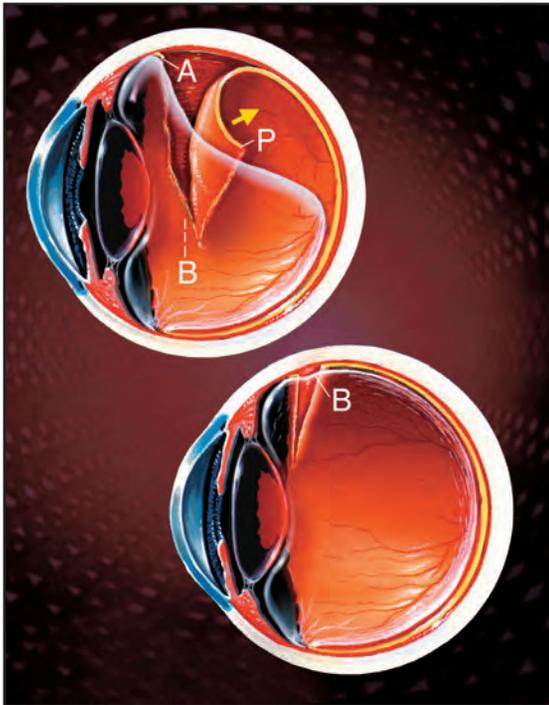


Figure 2: Comparison of Giant Tear and Dialysis - Pathogenesis. The top figure shows an example of a giant tear. Giant tears are defined as retinal breaks greater than 90 degrees in circumference. The vitreous gel is attached to only the anterior flap of the tear. Notice that the giant tear shown occurs at the posterior border of the vitreous base (B). The vitreous gel is attached to the anterior flap of the retinal tear (A) but is not attached to the posterior flap (P). This allows the posterior flap to move independently of the anterior flap; it can fold backward (arrow) and invert. By comparison, in the dialysis type tear shown in the lower figure, the vitreous gel (B) is attached to the tear. There is no movement or inversion of the tear. (Art from Jaypee Highlights Medical Publishers.)

Differences Between Giant Retinal Tears and Retinal Dialysis

Giant retinal tears occur at the posterior border of the vitreous base. The vitreous gel is not attached to the posterior flap, which moves independently of the anterior flap. The posterior flap can therefore fold backward and invert. In contrast, in a retinal dialysis the gel is attached to the retina posterior to the break; consequently, there is no inversion of the posterior flap (Figure 2). In retinal detachments associated with dialysis, the posterior hyaloid is usually attached, and epiretinal membrane proliferation and contraction are uncommon. Giant retinal tears, on the other hand, are almost always associated with posterior vitreous detachment and often associated with dispersion of pigment epithelial cells. Fibrocellular proliferation can easily occur on the retinal surfaces and the vitreous gel (Figure 3). Therefore, proliferative vitreoretinopathy (PVR) is a common sequel of giant retinal tear, which makes surgical management more challenging and the prognosis worse.⁵

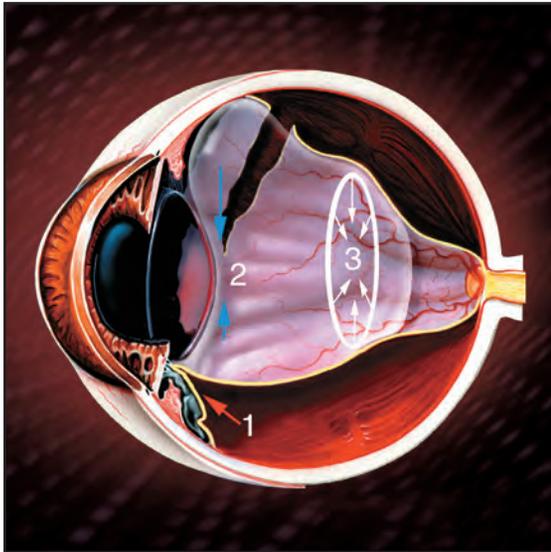


Figure 3: Forces Involved in Cases of Giant Tear with PVR. Proliferative vitreoretinopathy (PVR) can occur as a result of a giant retinal tear. PVR has anterior and posterior components. In the anterior component, the types of traction forces are: 1.) Anteroposterior traction which displaces the posterior insertion of the vitreous base forward. It is recognized by posterior retraction of the iris and a circumferential trough anteriorly at the vitreous base. 2.) Anterior circumferential traction is caused by proliferative tissue on the posterior border of the vitreous, creating a circumferential ring at the posterior border of the vitreous base. It is recognized by radial retinal folds extending posteriorly from the posterior border of the vitreous base. 3.) Anterior perpendicular traction is caused by proliferation within the vitreous gel. This transvitreal traction pulls the anterior retina to the center of the vitreous cavity causing an anterior funnel shaped retinal detachment. Posterior PVR occurs posterior to the posterior border of the vitreous base. (Art from Jaypee Highlights Medical Publishers.) (Art from Jaypee Highlights Medical Publishers.)

Preoperative Assessment of the Retinal Tear

The surgical approach should be guided by a preoperative study of the retina to determine the characteristics of the giant retinal tear (Figure 4). Using a slit lamp, the surgeon needs to determine the mobility of the vitreous and the degree of pigmentary dispersion.

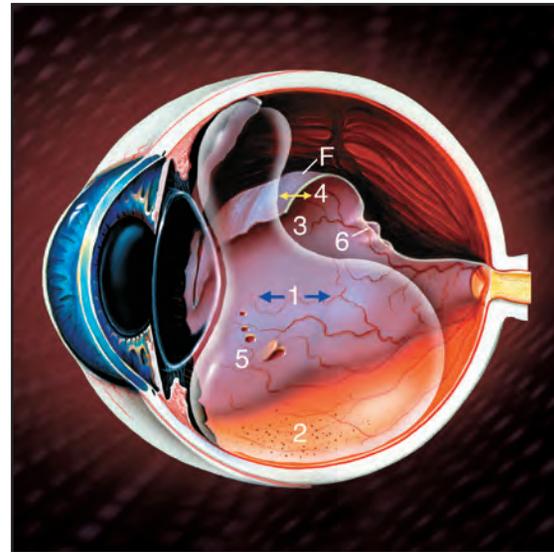


Figure 4: Preoperative Assessment of Retinal Tear Characteristics. Preoperatively, the surgeon needs to determine the mobility of the vitreous (1-arrow) and degree of pigmentary dispersion (2). The relationship (3) between the vitreous and the edge of the retinal flap (F) is noted. The mobility of the retinal flap is determined (4). Presence of additional small retinal breaks and tears (5) is assessed. The presence of periretinal proliferation is also determined (6). (Art from Jaypee Highlights Medical Publishers.)

The relationship between the cortical vitreous and the hyaloid posterior to the edge of the retinal flap should be noted (Figure 4). When the cortical vitreous has migrated under the inverted posterior flap of the tear, vitrectomy is necessary.⁶⁻⁸ In eyes in which the posterior hyaloid has not completely separated from the retinal surface opposite the tear, vitrectomy with a gas tamponade should be considered.

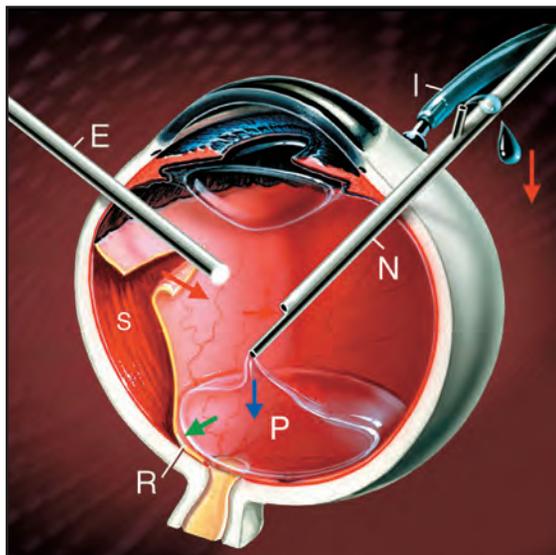


The mobility of the retinal flap must also be assessed. Vitrectomy is always necessary when the posterior flap is immobile. If the anterior edge of the tear is rolled, then the presence of epiretinal or subretinal proliferation should be suspected.

Although our main focus is on giant retinal tear, the surgeon should also look for the presence of additional small retinal breaks that should be treated with either laser or cryotherapy. A scleral buckle can be used alone without vitrectomy if the extent of the giant retinal tear is 120° or less and the posterior flap is not inverted.⁹ Scleral buckling alone can also be considered for a large retinal dialysis.

Surgical Principles for the Management of Uncomplicated Giant Retinal Tears

The surgical technique should be individualized for each case but follows the same



general outline and principles in most patients. The state-of-the-art treatment of giant retinal tears with or without PVR involves the use of perfluorocarbon (PFC) liquids. Using these liquids not only makes surgery simpler, but it also allows the surgeon greater confidence in planning the surgery and greater intraoperative control.¹⁰

THE IMPORTANCE OF PERFLUOROCARBONS

Pioneered by Stanley Chang, M.D., PFC liquids have revolutionized vitreoretinal surgery. They are derived from hydrocarbons and are created by replacement of the hydrogen atoms by fluorine atoms. They are inert, colorless substances with very low water solubility. Most importantly, they are heavier than water and have a specific gravity approximately twice that of water.¹¹ After intraocular injection of PFC liquid, the flattening forces are significantly greater than can be achieved with other materials used in vitreoretinal surgery, such as oil or gas (Figures 5, 6). Therefore, they facilitate dissection of membranes by flattening or stretching out the retina, particularly in the periphery.¹⁰ They are frequently used in the surgical management of giant retinal

Figure 5: Retinal Reattachment With Perfluorocarbon Liquid in Case of Giant Tear - Stage 1. In the case of retinal detachment with giant retinal tear, perfluorocarbon liquid (P) is injected into the vitreous cavity via the Chang cannula (N). Because the liquid has a specific gravity greater than water, it gravitates (blue arrow) to the posterior pole. This forces the subretinal fluid (S - red arrows) out through the giant retinal tear and out of the eye via the Chang cannula. The retina (R) is being forced to reattach (green arrow) in this manner. Infusion cannula (I). Endoilluminator (E). (Art from Jaypee Highlights Medical Publishers.)

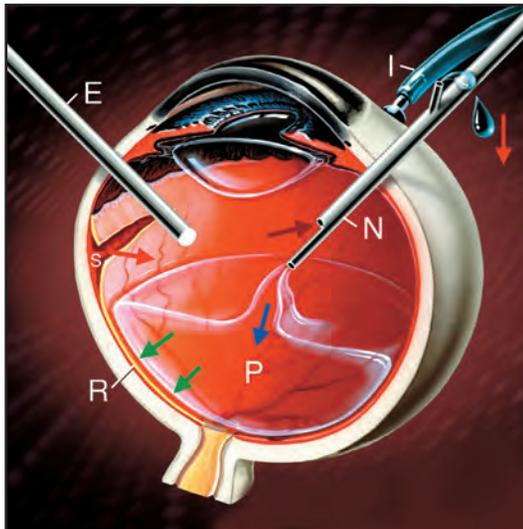


Figure 6: Retinal Reattachment With Perfluorocarbon Liquid in Case of Giant Tear - Stage 2. As more perfluorocarbon liquid (P - blue arrow) is injected into the vitreous cavity via cannula (N), the subretinal fluid (S) is forced out (red arrows) from behind the detached retina into the vitreous cavity and out of the eye via the cannula. The retina (R) is reattached (green arrows). Infusion cannula (I). Endoilluminator (E). (Art from Jaypee Highlights Medical Publishers.)

tears and PVR. They are also of great value in surgery of dislocated crystalline lenses or intraocular lenses, drainage of suprachoroidal hemorrhages, and retinal detachment associated with vitreous hemorrhage, especially when the retinal tear is hidden by blood.

Perfluorocarbon Liquids of Choice

Among the PFC liquids that have been described for treating complicated retinal detachments and giant retinal tears, most surgeons prefer to use perfluoro-n-octane because of its physical properties.¹³ Perfluoro-n-octane has a molecular weight of 438 daltons, a specific gravity of 1.76, a surface tension of 14 dynes per centimeter at 25 degrees Celsius,

a refractive index of 1.27, a vapor pressure of 50 mm Hg at 37 degrees Celsius, and a viscosity of 0.10 centistokes at 25 degrees Celsius. Perfluoro-n-octane has greater visibility during surgery, lower viscosity, and higher vapor pressure when compared to perfluorodecalin and perfluorophenanthrene, making it the ideal PFC for vitreoretinal surgery.

The greater visibility is important because it enables the surgeon to differentiate the perfluoro-n-octane from balanced salt solution (BSS). This allows the vitreoretinal surgeon to monitor the PFC level during intraoperative injection and obtain a more complete removal, which is required due to the long-term toxicity of these liquids. In addition, it enables the surgeon to remove the BSS from the edge of peripheral tears during fluid-air exchange, thereby preventing the ingress of BSS into the subretinal space. This differentiation is not visible with other PFCs because their refractive index is closer to water.

The lower viscosity of perfluoro-n-octane is important because PFC liquids with higher viscosity are difficult to inject and remove from the eye. Sometimes it is advantageous to inject the PFC liquid rapidly, which is easier with a liquid of lower viscosity. But most importantly, it is critical to remove all the PFC liquid from the eye. This substance is not used as a long-term intraocular tamponade, although it has been shown in a few reports to be safe and effective as a short-term tamponade.¹⁴⁻¹⁸ Experimental, electrophysiological, and histological studies in human and rabbit eyes have demonstrated that PFCs can be toxic to the retina, particularly when they remain in the eye in large quantity or for a long period of time.¹⁹⁻²³ The cornea can also become edematous in areas of contact



with the PFC liquid. Therefore, a complete replacement of the vitreous by PFC liquid for long-term use is not advisable.

Finally, the higher vapor pressure of perfluoro-n-octane allows a small residual amount of the liquid to evaporate during the fluid-air exchange and in the early postoperative period, which is another reason why it is currently the preferred PFC.

Indications for Perfluorocarbon Liquids

Although PFC liquids may be used in the repair of all retinal detachments associated with giant tears, they are particularly indicated in the following scenarios: giant tears in which the posterior margin of the tear has inverted and must be unrolled during vitrectomy surgery, giant tears complicated by moderate or severe degrees of PVR, and traumatic giant tears associated with vitreous or retinal incarceration into the wound or with severe subretinal hemorrhage. The main advantage of PFC liquids as an intraoperative “tool” is that they limit the need to manipulate the retina mechanically. Therefore, the risk of potential complications such as hemorrhage, retinal tears, and re-proliferation is significantly reduced.

Using PFC liquids in eyes that have giant retinal tears with PVR also allows the surgeon to identify residual epiretinal or subretinal membranes in the equatorial region and to perform the operation with the patient in a supine position, thus avoiding the need for rotational tables or beds and intraoperative prone positioning as in the pre-PFC era.²⁴

Surgical Technique for Uncomplicated Giant Retinal Tears

Removing the Basal Vitreous Gel Before Injecting Perfluoro-n-octane

To completely remove the basal vitreous gel, the lens most often needs to be removed even if it is clear. The surgeon performs a pars plana lensectomy, taking care to remove completely the posterior capsule (if an intraocular lens is not going to be placed). Then, using the vitreous cutter, he or she performs a total posterior vitrectomy. With scleral depression, the basal vitreous gel is debulked for 360 degrees (Figure 7). Then the surgeon injects perfluoro-n-octane using a panoramic

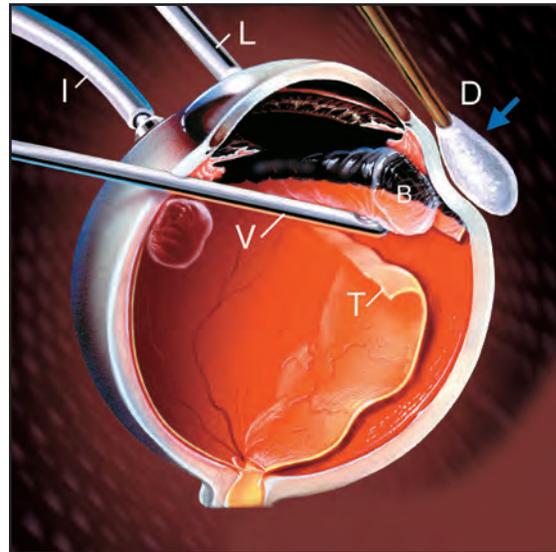


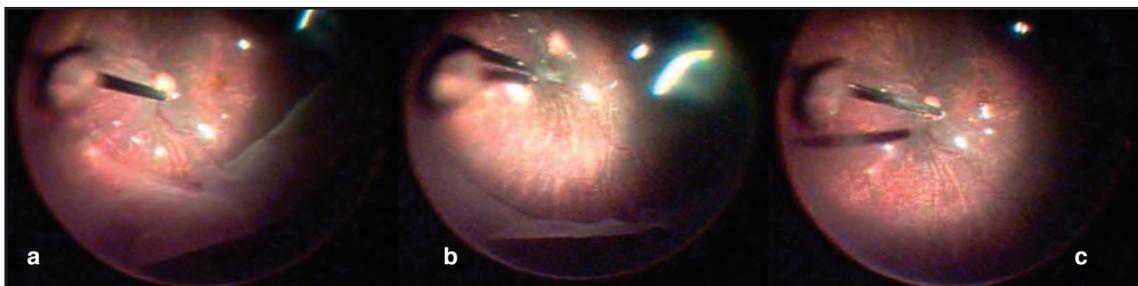
Figure 7: Technique for Removing Basal Vitreous. The central vitreous gel and lens are removed before injecting perfluorocarbon liquid. After the lens is removed, a total posterior vitrectomy is performed. With the aid of scleral depression (D), the basal vitreous gel (B) is debulked as shown for 360 degrees using a vitreous cutter (V) through the pars plana. Note the giant tear (T). Infusion cannula (I). The light pipe (L) is placed over the cornea to provide illumination. (Art from Jaypee Highlights Medical Publishers.)

wide-field viewing system. The Chang cannula is used to inject the PFC liquid very slowly over the optic nerve head (Figure 8). The volume of PFC liquid in the vitreous cavity is increased in a controlled, slow way to unroll the inverted posterior retinal flap, allowing the retina to return to its normal anatomic position²⁵ (Figure 9a-c). The PFC

liquid is not brought above the giant retinal tear unless the surgeon is certain there is no residual traction. Otherwise, the PFC liquid can migrate under the retina. Even if a small bubble remains under the retina, it can be toxic and can lead to a scotoma postoperatively.²⁰

Figure 8: Use of Wide-Field Lens During Injection of Perfluorocarbon Liquid

Using panoramic wide-field viewing system (L), the perfluorocarbon liquid (F) is injected slowly over the optic nerve via a Chang cannula (C). The 130 degree field of view (dotted line) allows optimal viewing as the volume of the PFC liquid in the vitreous cavity is increased (blue arrows-1,2,3) to unroll (red arrow) the inverted posterior giant tear flap peripherally. The retina is returned to its normal anatomic position. Infusion cannula (I). Endoilluminator (E). (Art from Jaypee Highlights Medical Publishers.)



Figures 9a, 9b, and 9c: a) Intraoperative Photos of PFC Liquid Flattening of the Rolled Posterior Flap of a Giant Retinal Tear (Surgeon's View). b) The inverted posterior flap of the superior giant retinal tear is slowly unfolded by injecting PFC liquid over the optic nerve. c) This results in complete flattening of the posterior flap to which endolaser can be applied prior to PFC-air exchange. (Images courtesy of Franco M. Recchia, MD)



Removing the Anterior Flap and Liquid-Air-Gas Exchange

After the PFC liquid completely reattaches the retina, many surgeons advocate excision of the anterior flap of the giant retinal tear with the vitreous cutter (Figure 10). The anterior flap is removed to prevent it from migrating anteriorly and exerting traction on the ciliary processes, which could lead to hypotony despite retinal reattachment. Removing the anterior flap also prevents the ischemic retina from leading to iris neovascularization. Once the retina is reattached and the anterior flap has been removed, endophotocoagulation is

used through the PFC liquid to treat the giant retinal tear and any other retinal breaks that may be present. It also is suggested that the laser treatment be extended at least one clock hour beyond the margins of the giant tear, because the giant tears often extend circumferentially.

Following endophotocoagulation, a PFC liquid-air exchange is performed, and care is taken to remove all fluid before removing the PFC liquid (Figure 11). It is very important to dry the edge of the giant retinal tear to prevent slippage of the posterior flap. After the fluid is removed above the PFC liquid

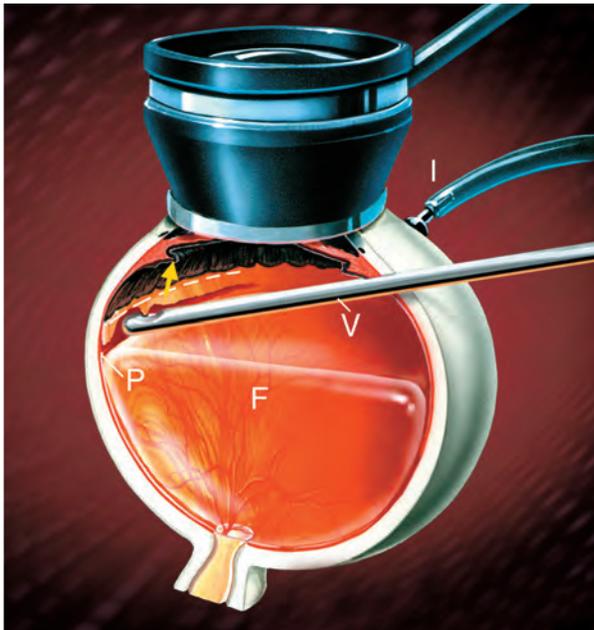


Figure 10: Technique for Removing the Anterior Flap of the Giant Retinal Tear. Once the posterior flap (P) of the giant tear has been repositioned using PFC liquid (F), the vitreous cutter (V) is used to remove the anterior flap as shown. This will prevent later displacement of the anterior flap anteriorly (arrow). The anterior flap will be removed to about the position of the dotted line (ora serrata). Note that the level of PFC liquid is not brought above the giant tear unless the surgeon is certain there is no residual traction. Infusion cannula (I). (Art from Jaypee Highlights Medical Publishers.)

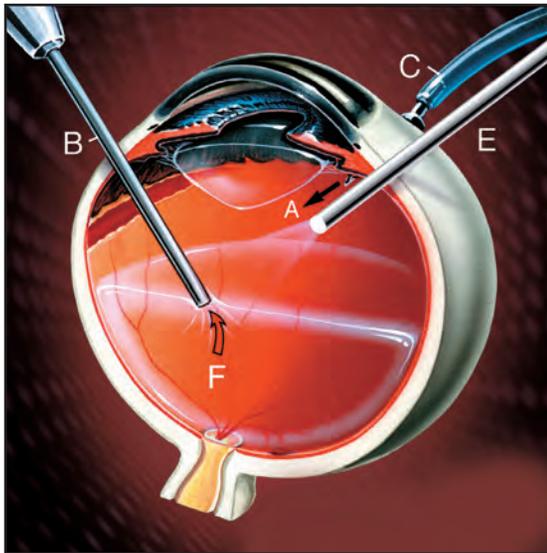


Figure 11: Technique of Perfluorocarbon Liquid / Air-Gas Exchange. First, all intraocular fluid is removed above the level of the PFC liquid and the giant retinal tear, and exchanged with air (A - black arrow) entering through an infusion cannula (C). With the giant tear dry, the PFC liquid (F) is then removed (red arrow) posterior to the giant tear via an aspiration cannula (B) as air continues to fill 100% of the cavity. If the fluid anterior to the giant tear is not removed prior to removing the perfluorocarbon liquid, slippage occurs. Endoilluminator (E). (Art from Jaypee Highlights Medical Publishers.)

and the edge of the giant retinal tear is dried, the liquid is removed while air is entering the eye through the infusion cannula. The surgeon must take care to remove all the small bubbles of residual PFC liquid that remain on the epiretinal surface. With perfluoro-n-octane, it is very easy to visualize these small residual bubbles. Finally, an air-gas exchange is performed with a non-expansile concentration of perfluoropropane gas. This can be performed by injecting the

gas through the infusion cannula and venting air through an open sclerotomy. Another technique involves closing all sclerotomies, injecting the gas via a 30-gauge needle, and venting with a 27-gauge needle through the pars plana. The latter technique allows for greater control of intraocular pressure by avoiding the sudden loss of gas that one may encounter when removing the infusion cannula. The use of a panoramic wide-field viewing system greatly facilitates performing most of the intraocular steps of the surgery. At the end of the procedure, the conjunctiva is closed, and the patient is positioned appropriately to allow the optimal gas tamponade of the giant retinal tear.

The Scleral Buckle Controversy in Giant Tears Without PVR

An important controversy in the treatment of giant retinal tears without PVR is whether or not to place an encircling scleral buckle. Many surgeons only place scleral buckles in eyes with PVR or in eyes at significant risk for developing PVR (Figure 12). These include eyes with marked retinal pigment epithelial cell dispersion into the vitreous, preoperative choroidal detachments, or star folds in the retina.

If a scleral buckle is not placed, the surgeon must be sure to have released all potential traction, shave the vitreous base 360 degrees (Figure 8), and try to ensure that the patient will not need re-operation or that the retina will not re-detach. The main causes of re-detachment following giant retinal tear surgery include the development of PVR and folds along the giant retinal tear that allow

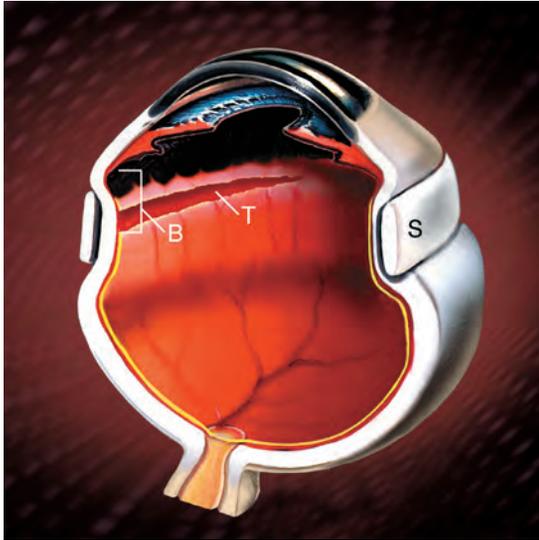


Figure 12: Scleral Buckle in Cases of Giant Tear with PVR or Potential PVR. This example shows the proper placement of a wide, broad and moderately elevated scleral buckle (S) in the case of a giant tear. The 7mm silicone exopant is placed to cover the entire vitreous base (B), including the posterior border. Note the giant tear (T). The scleral buckle is placed to support the non-torn retina. (Art from Jaypee Highlights Medical Publishers.)

vitreous fluid to leak through and re-detach the retina.^{5,6} These folds may be caused by persistent traction from basal vitreous gel. If the crystalline lens is not removed and the basal vitreous gel is not debulked, a circumferential scleral buckle should be employed.^{26,27}

Surgical Technique for Giant Retinal Tear with PVR

Patients with giant retinal tears with PVR or a high likelihood of developing PVR are frequently managed with a scleral buckle accompanying the vitrectomy. A scleral buckle is typically not used to close a standard giant

retinal tear because the traction has already been released (the vitreous is not attached to the posterior flap), and no connection exists between the tear and the anterior retina. The rationale to use a scleral buckle is to support the non-torn retina. A 7 mm silicone exopant buckle is generally broad enough to cover the entire vitreous base, including the posterior border (Figure 12).⁹ If the patient does not have anterior PVR and the lens is clear, the lens can remain in the eye.

If the patient has anterior PVR or the lens is not clear, however, a pars plana lensectomy with complete removal of the posterior capsule should be performed. If the lens is not removed, the vitreous base cannot be completely debulked (Figure 8). In these cases, a scleral buckle will counteract some of the anterior traction.

Removing Epiretinal Membranes

In patients with giant retinal tears associated with PVR, it is important to remove as many posterior epiretinal membranes as possible prior to injecting PFC liquid.²⁸ Bimanual dissection using an illuminated pick and a mini-diamond tip forceps often is effective in removing epiretinal membranes while minimizing iatrogenic retinal breaks. Once most or all of the epiretinal membranes have been removed, the perfluoro-n-octane is injected over the optic nerve head to open retinal folds, to unfold the posterior flap of the giant retinal tear, and to allow better visualization of areas with residual preretinal or subretinal membranes. The posterior flap of the giant retinal tear is stabilized as more PFC liquid is injected. The edge of the tear is examined as the PFC liquid bubble approaches it. Epiretinal or subretinal membranes present



Figure 13: Technique for Removal of Epiretinal Membranes on the Inner Surface of the Posterior Edge of a Giant Tear. As perfluorocarbon liquid (F) is injected, the edge of the posterior flap (P) of the giant tear is monitored. Resistance to unfolding by the PFC liquid may give a clue to the presence of epiretinal membranes on the inner surface of the posterior edge of the tear. Epiretinal membranes (M) on the inner surface may give the edge a rolled appearance and can cause a circumferential shortening along the edge. These membranes should be dissected with a vitreoretinal pick as shown, or if this is not possible, excised. Panoramic viewing lens (L) and infusion cannula (I). (Art from Jaypee Highlights Medical Publishers.)

on the inner surface of the posterior edge of the giant retinal tear are identified by a rolled appearance of this edge. These membranes can cause a circumferential shortening along the edge of the retinal tear and should be opened by dissection or excision using the vitreous cutter (Figure 13). *Additional PFC liquid is injected until the level lies just posterior to the margin of the tear.* The large volume of PFC liquid stabilizes the retina and allows close trimming of the peripheral or basal vitreous gel. With traditional viewing systems, the retinal edge may disappear from the field

of view of the operating microscope as the retina is flattened. The use of a panoramic viewing system offers the advantage of obtaining a wide field allowing observation of the entire retina during PFC injection and removal, facilitating endophotocoagulation. Small radial or circumferential folds that have flattened along the edge of the tear can be gently smoothed using a spatula.

Some cases of more chronic retinal detachment associated with a giant tear will have extensive subretinal proliferation. In these cases, it will be necessary for the surgeon to dissect the subretinal membranes prior to the injection of PFC liquid. On occasion, it may be necessary to enlarge the giant tear in order to gain better access to the subretinal space.

The remainder of the operation is the same as the procedure for giant retinal tear without PVR. The giant retinal tear is treated with endophotocoagulation while the PFC liquid is still in the eye. Then a PFC liquid-air exchange is performed. The air is subsequently exchanged for gas.

Silicone Oil Controversy

In addition to the scleral buckle controversy, the other major unresolved issue in treatment for giant retinal tears concerns the choice of a long acting gas like perfluoro-propane or silicone oil as the intraocular tamponade.²⁹⁻³¹ Indications for silicone oil in patients with giant retinal tears are the same as in patients with PVR: patients who need to travel by air, children who cannot be positioned prone postoperatively, patients whose back or neck conditions preclude prone positioning after surgery, and monocular patients who require better vision immediately.³¹



Surgical Results

The two largest, prospective, multicenter case series utilizing PFC liquids in the management of giant retinal tears were performed by Scott et al. and Kertes et al. These studies revealed recurrent detachment rates of 49% and 30%, and final attachment rates of 91% and 79%, respectively. Preoperative characteristics portending a greater risk of recurrent detachment in both studies included larger size of retinal tear and preoperative PVR.^{13,15} As expected, patients with uncomplicated giant retinal tears demonstrated better visual results than patients with preoperative PVR.¹⁵ As in other types of retinal detachment, *the main complication or cause of failure in the management of giant retinal tears is the development of PVR following surgery and the need for re-operation.*^{5,6}

Traditionally, scleral buckles have been used in the management of giant retinal tears.^{7,9} In 1969, Norton and colleagues became the first not to use a scleral buckle in the treatment of giant retinal tears. Instead, they used an intraocular air bubble.³² Kreissig and colleagues successfully reattached the retina in five eyes of patients with giant retinal tears using a retrohyaloidal injection of gas without vitrectomy or scleral buckling.³³ The use of pneumatic retinopexy without scleral buckling or vitrectomy was also reported by Irvine and Lahey.³⁴ Several authors have reported using vitreous surgery without concomitant scleral buckling in the treatment of giant retinal tears. Leaver and colleagues used vitrectomy and silicone oil injection without scleral buckle in some of the eyes reported in their series.³⁵ Hoffman and Sorr reported successful reattachment in 6 eyes with giant retinal tears using vitrectomy and perfluoropropane gas

without scleral buckling.³⁶ Chang and associates repaired 6 eyes with giant retinal tears without scleral buckling using vitrectomy with PFC liquid and intraocular gas.³⁷ Ambresin and colleagues reported successful reattachment in 16 of 18 patients with giant retinal tears using 360-degree laser photocoagulation in conjunction with vitrectomy and silicone oil tamponade, but without scleral buckling.³⁸ Kreiger and Lewis described a series of 11 patients with uncomplicated giant retinal tears treated with vitrectomy, radical dissection of the vitreous base, injection of perfluoro-n-octane, endophotocoagulation, PFC liquid-air exchange, but no scleral buckle. Initial and final retinal attachment rates in this series were 91% and 100%, respectively.³⁹

In summary, the ideal surgical technique for uncomplicated giant retinal tears would be one that would achieve intraoperative and long-term retinal reattachment without complications or a need for re-operation. There is almost universal agreement that the surgical technique should include pars plana vitrectomy, PFC liquids, and photocoagulation while viewing the fundus with panoramic systems. This allows for excellent anatomic re-apposition of the flap, the avoidance of slippage, and limited dispersion of the retinal pigment epithelial cells. Ultimately, this leads to a decreased risk of proliferation, recurrent retinal detachment, and re-operation. Controversy continues about whether giant retinal tears without severe PVR require scleral buckling and lensectomy. Scleral buckling provides advantages including supporting non-torn retina at the vitreous base and reducing the risk of further tearing. The disadvantages include the possibility of promoting slippage or retinal folding which could possibly lead to re-detachment and cause more surgical



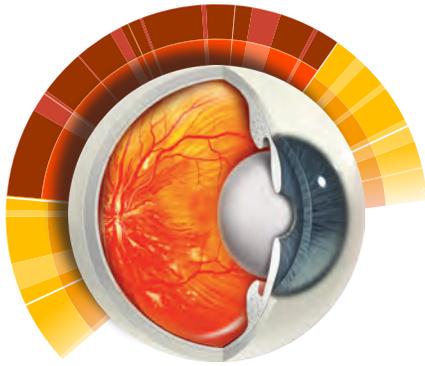
trauma. In cases in which a scleral buckle is not used, lens removal allows for the debulking of the basal vitreous gel and reduces vitreoretinal traction, decreasing the rate of recurrent retinal detachment and re-operation.

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Proliferative Vitreoretinopathy Clinical, Pathophysiological and Therapeutic Considerations

JUSTUS G. GARWEG, MD

Background

With the advances in vitreoretinal surgery, the success rate of retinal detachment surgery has grown to more than 90%. The development of proliferative vitreoretinopathy (PVR) is the major cause for failure.¹ The Retina Society Terminology Committee (1983). PVR comprises a tissue destructive complication of rhegmatogenous retinal detachment (RD), severe ocular trauma, or intraocular surgery in a frustrating attempt to stabilize the residual function. As such, the response is unspecific and not principally different from that resulting from proliferative intraocular disorders of other origin, namely chronic retinal ischemic diseases such as diabetic retinopathy and retinopathy after central retinal vein occlusion or due to retinopathy of prematurity. Untreated, it will result in progressive and profound intraocular scarring leading to to-

tal retinal and ciliary body detachment and thereby blindness and phthisis. PVR is the most serious complication of failing retinal reattachment surgery and beyond the leading causes of vision loss in developed countries. It is a complex process of events that may comprise a tissue-specific form of a wound healing response with inflammation, migration and proliferation of a variety of cells. The resulting membranes can exert traction and reopen previously closed retinal breaks, create new breaks, and distort or obscure the macula. In the early part of the last century the success rate of retinal reattachment surgery was virtually zero, and it was Jules Gonin who understood RD as a consequence of vitreous detachment and forces resulting in retinal tears and traction. He successfully proved his understanding of the pathophysiology of retinal detachment consequently with a treatment aiming at closing retinal breaks, thereby increasing the surgical success rate



to more than 60%.² To further increase the final success rate in the treatment of retinal detachment, a better understanding of the risk factors for PVR is needed in patients presenting with acute retinal detachments. Principally three categories of risk factors have to be differentiated, i.e. preoperative eye and patient related risks, best surgical management, and the use of adjuvant therapies.³

The risk of PVR has been reported to vary between 10 and 40% depending on the underlying disease and the situation prior to PVR surgery. Beyond the factors of influence on the development of PVR, surgical technique and skills play the key role, but adjunctive measures such as pharmacological adjuncts and the choice of material for vitreous replacement may significantly add to the outcome.⁴ At the end of the day, PVR remains a difficult management problem despite all recent advances in vitreoretinal surgery. Surgery for PVR now has a relatively high anatomical success rate but visual results are frequently less striking.⁵ After 30 years of slow progress, the use of adjunctive treatments to prevent cellular proliferation holds still the strongest promise for prevention and recurrences of PVR after surgery.

This overview provides information about the current understanding of the disease and its stages, an analysis of underlying risk factors, therapeutic options and preventive measures.

Definition and Causes

Retinal detachment results from the separation of the neurosensory retina from the underlying retinal pigment epithelium (RPE). Both layers are of neuroepidermal origin, but they do not have a direct anatomical connection.⁶ Therefore, attachment of neuroretina and PRE is not strong, allowing the laminar space between the two layers to grow upon tractional forces. Once the retina has separated from the RPE and retinal detachment is evolving, the outer retina becomes ischemic due to the loss of its blood supply from the choroid. Moreover, the biochemical exchange between RPE and retinal photoreceptors is interrupted, resulting in the accumulation of subretinal fluid with loss of photoreceptor outer segments, until at the end the entire photoreceptor cell layer becomes atrophic.^{7,8} In this context, PVR may be understood as a complex process of tissue induced events including inflammation, migration and proliferation of several types of merely locally derived cells.^{9,10,11} These grow to cellular membranes which contract within the vitreous, and on retinal sur- and backfaces.¹² As such they are not principally different from membranes driven by other sources and forces such as proliferative diabetic or ischaemic retinopathy or trauma.¹³ The term proliferative vitreoretinopathy represents a morphological description of the clinically observed process of proliferation involving vitreous cavity and

the retina. PVR was first reported by Gonin (1934) who described his observation as a form of preretinal organisation, as an invasion of the retinal surface by membranes that do not modify the retinal structure. Machemer (1978) proposed a classification of what he termed massive periretinal proliferation,¹⁴ which served the basis for the nowadays widely used classification of retinal detachment with proliferative vitreoretinopathy (Table 1).¹⁵ This grading system has the great advantage of being simple and widely applicable, but

it does not include important factors such as duration of disease, distinction between pre-operative and postoperative PVR, the number and location of retinal breaks, the location of vitreoretinal tractional ring formation, the degree of contraction of vitreous base etc, all of which may be important for surgical strategy and functional outcomes. Therefore, an updated classification of retinal detachment with proliferative vitreoretinopathy was provided by Machemer and coworkers.¹⁶ This

<p align="center">Table 1 Classification of Retinal Detachment with Proliferative Vitreoretinopathy (PVR)</p>		
Grade	Name	Clinical Signs
A	Minimal	Vitreous haze, vitreous pigment clumps
B	Moderate	Wrinkling of the inner retinal surface, rolled edge of retinal break, retinal stiffness, vessel tortuosity
C	Marked	Full thickness fixed retinal folds
C-1		one quadrant
C-2		two quadrants
C-3		three quadrants
D	Massive	Fixed retinal folds in four quadrants
D-1		wide funnel shape
D-2		narrow funnel shape
D-3		closed funnel (optic nerve head not visible)
<p align="center"><i>(The Retina Society Terminology Committee. The classification of retinal detachment with proliferative vitreoretinopathy. Ophthalmology 1983;90:121-5)</i></p>		



modified classification and grading system has remained unchanged for the less severe stages (grade A and B) but attempted to more precisely describe location and severity of advanced PVR (grades C and D; Tables 2A and 2B). Due to its more complex character and eventually due to its less obvious prognostic relevance this classification has not found a

broad acceptance beyond vitreoretinal surgeons for routine purposes, but may well be helpful in PVR-treatment studies such as the silicone study.¹⁷ None of these classification schemes includes biologic activity of PVR, which may be beyond the clinically relevant factors for progression and treatment outcome.^{18,19,20}

Table 2A
Proliferative Vitreoretinopathy Described by Grade

Grade	Features
A	Vitreous haze; vitreous pigment clumps; pigment clusters on inferior retina
B	Wrinkling of inner retinal surface; retinal stiffness; vessel tortuosity; rolled and irregular edge of retinal break; decreased mobility of vitreous
C P 1-12	Posterior to equator: focal, diffuse, or circumferential full-thickness folds*; subretinal strands
C A 1-12	Anterior to equator: focal, diffuse, or circumferential full-thickness folds*; subretinal strands*; anterior displacement; condensed vitreous with strands
*Expressed in the number of clock hours involved	

(Reproduced according to Machemer R et al. An updated classification of retinal detachment with proliferative vitreoretinopathy. Am J Ophthalmol 1991; 112: 159-65)



Table 2B
Grade C Proliferative Vitreoretinopathy Described by Contraction Type

Type	Location (in relation to the equator)	Features
1. Focal	Posterior	Star fold posterior to vitreous base
2. Diffuse	Posterior	Confluent star folds posterior to vitreous base. Optic disk may not be visible
3. Subretinal	Posterior/Anterior	Proliferations under the retina: Annular strand near disk; linear strands; moth-eaten-appearing sheets
4. Circumferential	Anterior	Contraction along the posterior edge of vitreous base with central displacement of the retina; peripheral retina stretched; posterior retina in radial folds
5. Anterior displacement	Anterior	Vitreous base pulled anteriorly by proliferative tissue; peripheral retinal trough; ciliary processes may be stretched, may be covered by membrane; iris may be retracted

(Reproduced according to Machemer R et al. An updated classification of retinal detachment with proliferative vitreoretinopathy. Am J Ophthalmol 1991; 112: 159-65)

Clinical Presentation

The clinical features of PVR depend on the location of membranes. This in turn is related to the sites of vitreoretinal contact and traction, since the vitreous serves the surface line along which membranes tend to expand. Moreover, the vitreous is not rich regarding

nutritional factors if the uveovascular barrier is maintained. This results consequently in the selection and propagation of cells which do not require specific environmental conditions, i.e. fibroblasts.

Proliferation at the posterior vitreous surface may cause the development of membranes located at the equator or posteriorly.

Proliferation within the vitreous base and anterior cortex may result in anterior traction of the retina towards the pars plana, whereas membrane contraction on the posterior retinal surface may lead to distortional and irregular retinal folds generally referred to as star folds (Figure 1). These are more frequently found in the lower two thirds of the retina. Proliferation may also occur in the subretinal space as fibrous strands and plugs which are not specific of PVR and may well be observed in

other situations, namely after ocular trauma (Figure 2 A-B).²¹ Once not involving the macula, PVR itself is widely asymptomatic (Figure 3 A-C). Epimacular membranes lead to metamorphopsia and reduced vision (Figure 4 A-B). If PVR membranes contract they can reopen closed retinal breaks and induce new ones, thus leading to retinal redetachment (Figure 5). The mechanical impact on the retina may functionally present with photopsia, but usually remains undetected by the affected

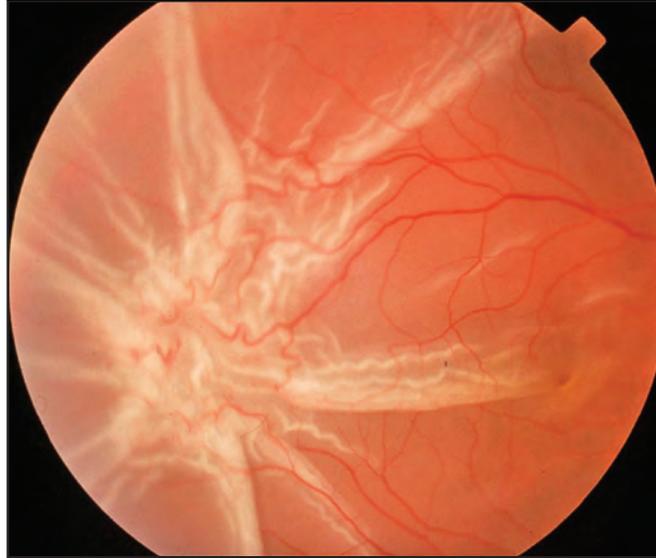


Figure 1: Typical image of a star fold in untreated primary retinal detachment.

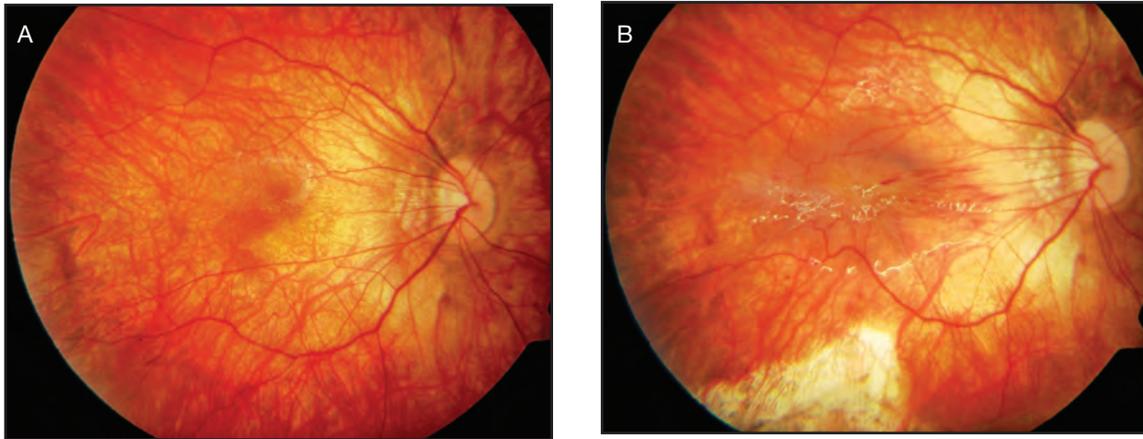


Figure 2 A and B: This epiretinal membrane developed four months after repair of a retinal detachment with ora dialysis which had developed secondarily to a blunt ocular trauma in a highly myopic eye 10 days before. Visual acuity was stable at this time (A). Two months later, a remarkable progression with proliferation and contraction of the membrane is to be observed (B), obviously reducing vision and limiting the functional reserve.

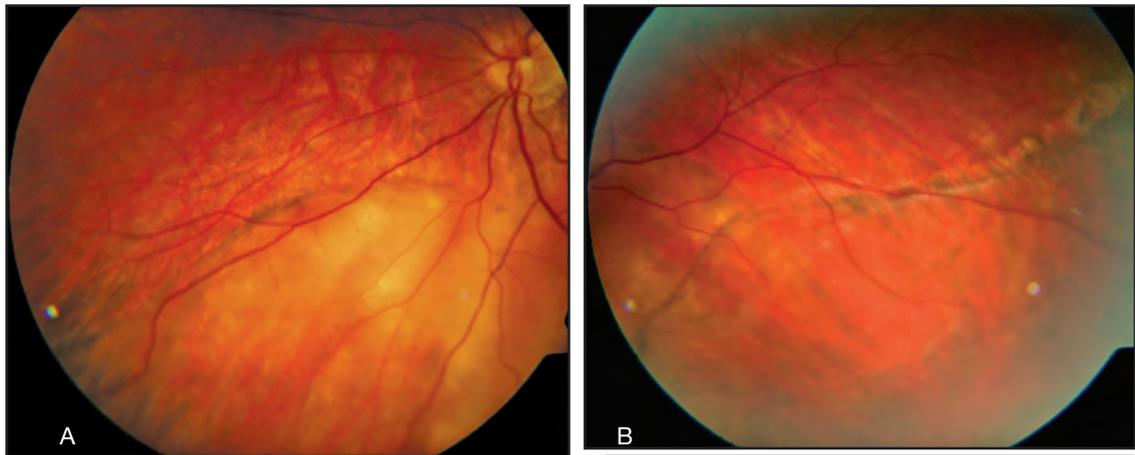
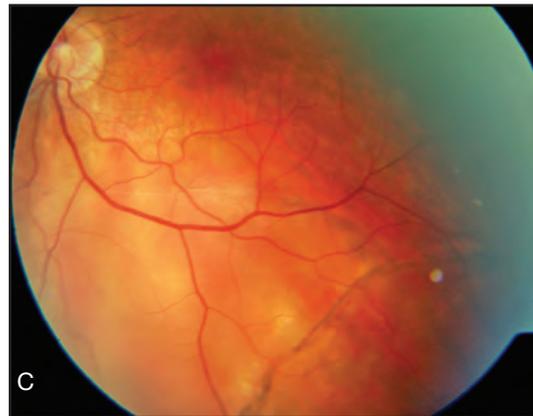


Figure 3 A - C: This subretinal fibrotic demarcation line along the central extension of an obviously elder and asymptomatic rhegmatogenous retinal detachment of the lower circumference represents an attempt of self-limiting the disease (A and B). Progression of the detachment towards centrally elevating the inferior vessel arcade enforced surgical intervention (C).



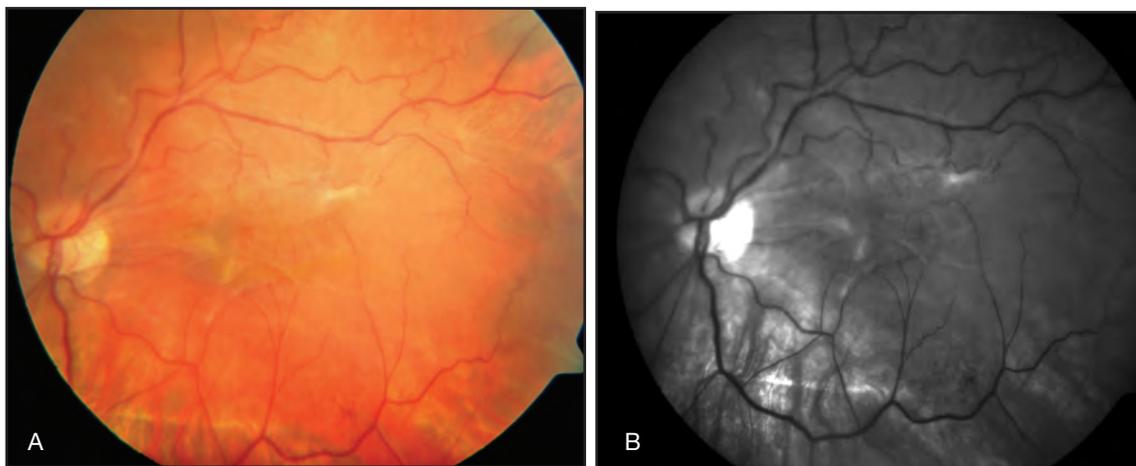


Figure 4 A and B: Same eye as in Figure 3. Extensive epimacular membrane developed three months after successful retinal detachment repair with vitrectomy, endodrainage, endolaser and SF6 gas tamponade. The extension of the membrane may much better be assessed from the red free (B) than the colour image (A). Only mild vessel distortion is indicative of as yet only mild retinal traction of an immature membrane.

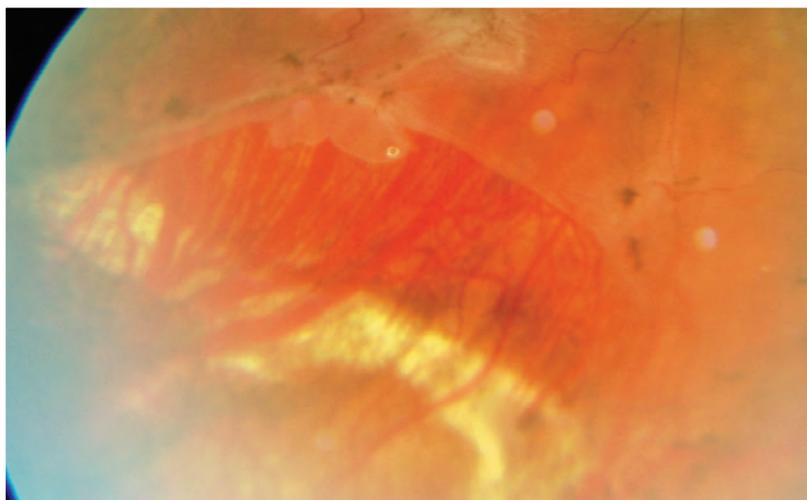


Figure 5: New retinal tear with irregular edges at the central margin of a laser scar secondary to periretinal proliferation with two beginning star folds and epiretinal pigment clusters.

individuals if not complicated by tractional retinal detachment. The progression of membrane formation and maturation may vary widely interindividually, making the prediction of progress difficult, but the expected activity of membranes determines the timing of surgical intervention. No systemic condition has been associated with the development of PVR, and there is no evidence for genetic factors interfering with wound healing.



Figure 6: Typical histological image of a PVR membrane (PAS, magnification 200x) with few cells of fibroblastic morphology, no vessels, barely any pigment or inflammatory cells (Image kindly provided by GM Sarra, Department of Ophthalmology, University of Bern).

Histology and Cell Biology of Wound Healing in PVR

It is clearly the tissue trauma resulting from separation of the neuroretina from the RPE which sets the stage for the development of PVR.²² Control of the biological process, which is involved in cell proliferation and retinal wound healing, might significantly enhance the success of retinal detachment repair and open the floor for nonsurgical therapeutic options. An early identification of cases at risk would allow to apply primary PVR prevention strategies and to control vitreoretinal proliferation prior to adopting surgical techniques. Thus, the knowledge of the pathological process and local environmental changes in response to RD and PVR may gain increasing interest within the next years.

The histological substrate of PVR are contracting cellular or fibrocellular membranes, which interfere with retinal function by progressive contraction^{23,24} (Figure 6). In contrast to membranes in diabetic or ischaemic retinopathies, PVR membranes typically contain retinal pigment epithelial cells, but no vasculature. The RPE cells in these membranes typically switch to a fibroblast- or macrophage-like cell morphology with fibroblastic cells more present in the contractile elements of those membranes.^{14, 25,26} There is currently no clue what factors drive the functional switch towards a fibroblastic dedifferentiation of RPE cells, which is also observed at a much slower rate in RPE cell culture. Neural ele-



ments may be detected in PVR membranes, but there is still considerable doubt about the role of the cell types involved. Mueller cells and retinal glial cells are consistently found in epiretinal membranes in PVR. However, their role in PVR has remained uncertain. They might reflect outgrowth from the retina into the developing membrane, resembling the capacity of these cells to respond to the environmental change, the capacity to proliferate, translocate from the retina and alter their phenotype and functional characteristics.²⁷ But their presence in consequence of the tissue damage resulting from membrane excision cannot be excluded.²⁸ It must be kept in mind that the cellular composition of PVR membranes may be altered by surgical intervention, namely in cases of recurrent retinal detachment and by the use of tamponades, namely silicone oil and heavy liquids.^{29,30} On this basis it has been suggested that the tamponade may attract macrophages which enhance PVR progression by accumulation of cytokines, namely macrophage derived growth factor, in the lamellar space between tamponade and retina. Fragments of the retinal inner limiting membrane are frequently found in PVR membranes. They may indicate the strong adherence between membrane and retinal surface, which explains their capability of inducing retinal breaks and detachment as well as the problems evolving in some cases during peeling them off the retinal surfaces.³¹

In an attempt to reconstitute or preserve visual function, PVR induces an active remodelling process in the retina. This is indicated by an upregulation of local environmental factors, i.e. growth factors and cytokines. Glial cells may be one important source of the growth factors, which potentially protect the neuroretina, but also can exacerbate the proliferative process. Principally, a functional recovery may be possible, but the outcome will result from the balancing between protective and destructive reparative mechanisms regulated by the same factors, and is merely driven by secondary pathology, namely photoreceptor damage due to periretinal gliosis.⁵

Pathophysiological Considerations

The pathogenesis of proliferative vitreoretinopathy is poorly understood. Retinal detachment resembles a form of tissue injury which induces a physiological cascade of wound repair mechanisms. This is generally divided in three phases: inflammation, proliferation and tissue remodelling and scar formation.³²

In general, the development of PVR may be understood as a three-phasic process of three overlapping phases (Table 3). In the first phase after trauma, migration of local,

i.e. RPE cells into the vitreous and subretinal space is induced. Glial cells may spread through the inner limiting membrane onto the retinal surface to give a strong connection allowing in a second phase the formation and contraction of a membranous tissue with the exudation of fibrin, elastin and fibronectin (Figures 5 - 9). Once stabilized, the attached cells start with collagen synthesis clinically delineated as maturation of the more and more compact membrane (Table 3). At this stage, the adherence of a PVR membrane may be strong, but surgical delamination of the membrane from the retina may be facilitated because of a better demarcation and visibility of membrane extension.

In the first phase, local inflammation provides the basis for vascular opening and outgrowth, allowing macrophages to remove

damaged tissue and cells, and serves as a basis for wound repair. Typically, a breakdown of the uveo-vascular barrier becomes evident by an increased Tyndall phenomenon, and in many elder cases, xanthochromatous, protein rich subretinal fluid may be observed during surgery. In this phase, several growth factors are activated, namely TGF beta (transforming growth factor beta), PDGF (platelet-derived growth factor) and EGF (epidermal growth factor) and many others. Polymorphonuclear cells are found from a few hours after detachment and release additional factors, namely FGF (fibroblast growth factor) to further attract monocytes, which are transformed to macrophages.³³ The second phase of wound healing, proliferation, may overlap widely with the first one. In this phase, macrophages stimulate the accumulation and proliferation of fibroblastic cells.³⁴ In the third phase, the

Table 3
Three Biological Phases of PVR Development

Cell migration (Grade A)	Retinal pigment epithelial cells migrate through a retinal break into the vitreous cavity
	Glial cells migrate onto the retinal surface
Contraction (Grade B)	Blood-retinal barrier damage leads to progressive exudation of blood compounds, i.e. fibrin, elastin and fibronectin, and growth factors and cytokines
Cell proliferation (Grades C - D)	Collagen synthesis becomes clinically visible in demarcated membranes producing traction to the retina



number of active cells decreases with maturation of the membranes, which is indicated by reorganisation of the extracellular matrix. At the end of this phase, fibroblasts contract,

which is clinically resembled by the typical pictures of macular pucker and star fold formation (Figures 7A and B).

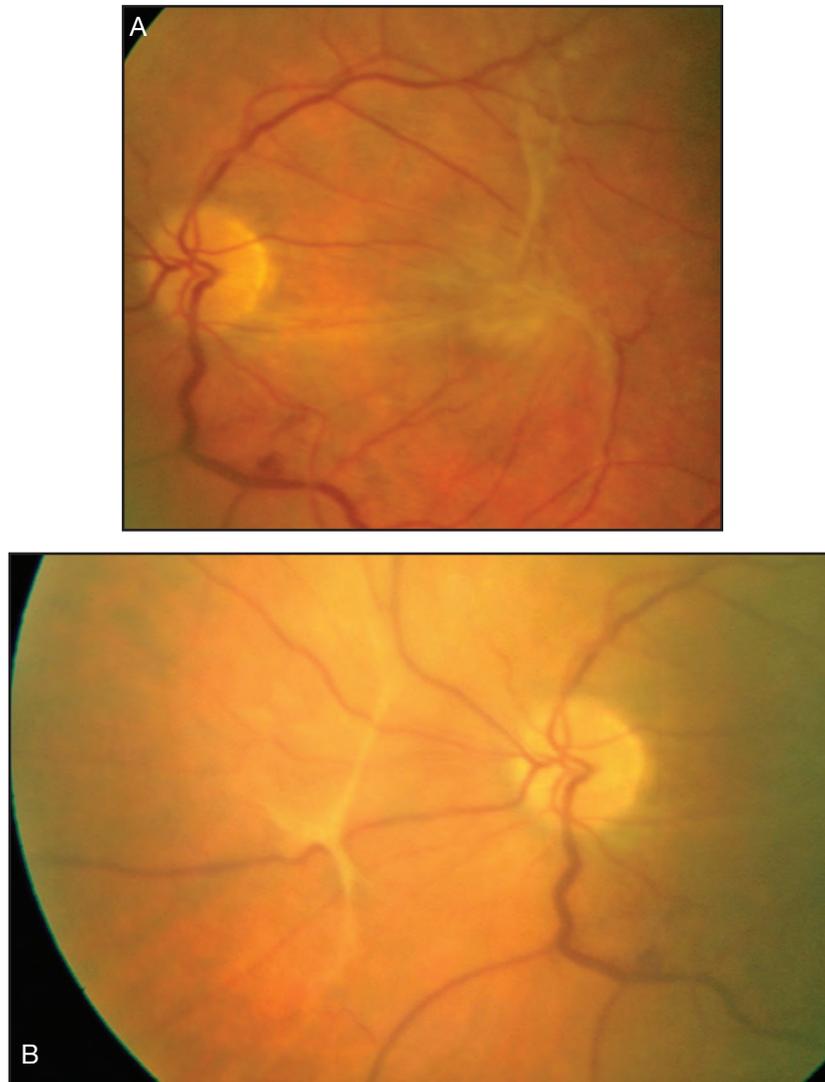


Figure 7 A and B: Extensive secondary epimacular membrane (A) and star fold formation (B) two months after successful reattachment surgery (vitrectomy, endodrainage, endolaser and cyroretinopexy) for primary rhegmatogenous retinal detachment.



Interestingly, PVR is not observed in the context of exudative retinal detachment despite its usually inflammatory origin with extensive vascular leakage.³⁵ This led to the conclusion, that it is the retinal break which induces the wound healing process and triggers PVR.¹⁸ The switch from the attempted wound healing of a retinal break towards the development of pathologic retinal wound healing, clinically referred to as PVR, is probably driven by the proliferation and functional metamorphosis of local cells such as hyalocytes, glial cells and RPE cells to fibroblasts.^{36,37} Multiple therapeutic attempts have been undertaken in order to control their proliferation with the use of antiproliferative and mitogenic agents, but these cells may hardly be influenced by any treatment without exposing the retina to a severe risk of toxic damage. Other cells involved in the reparative process, namely platelets, polymorphonuclear cells and macrophages, and inflammatory cells, i.e. lymphocytes which have been implicated in the pathogenesis of PVR, may thus be more feasible as pharmacological targets.^{38,39,40}

Local cell proliferation is unfortunately often overstimulated and the proliferating cells invade the vitreous.^{41,42} Several growth factors and more recently also matricellular proteins such as thrombospondin 1, tenascin, and secreted protein acidic and rich in cysteine (SPARC) which modulate the migration of RPE cells in the epiretinal membranes have been identified within the vitreous and periretinal membranes in eyes with PVR. Their biochemical proper-

ties, either enzymatic, chemotactic, mitogenic or proinflammatory, make them candidates for influencing the evolution of disease alone or in a synergistic way. They may interfere at different levels with cell migration, proliferation and vitreoretinal contraction. Immune mediated inflammatory reactions have also been described, and vitreoretinal strands may add to mechanical instability.

PVR typically begins at the edges of a retinal break, and first signs of PVR are the movement of pigmented cells through the hole into the vitreous cavity (tobacco dust, PVR grade A) and irregular and enrolled edges of the retinal break (PVR grade B; Figure 8). Once PVR has developed and progressed, its location is not associated with the inducing break. Instead, a break close to a fibrovascular proliferation may develop secondarily to traction.^{43a}

As already mentioned, chronic retinal ischemia may be an important motor for the development of PVR leading to retinal atrophy and fibrotic remodelling as known from vascular retinal disease, such as diabetes, retinal vein occlusion and retinopathy of prematurity. The separation of the retina from the RPE in consequence of retinal detachment leads to outer retinal ischemia in consequence of the loss of nutritional supply from the choroid. Early, photoreceptor outer segments die, and if retinal detachment persists, the complete photoreceptor cell layer becomes atrophic.⁸ In

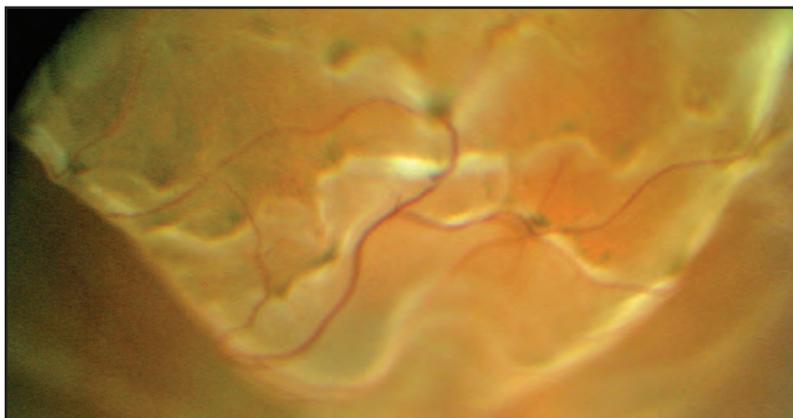


Figure 8: Pigmented cells and a Tyndall phenomenon resembling tobacco dust may be observed in the retrolental vitreous (PVR grade A) using the slit lamp indicating the presence of retinal tear and blood-retinal barrier breakdown. Here, pigment clusters are visible in the subretinal space together with retinal vessel wrinkling (PVR grade B; picture).

the second phase, cystic retinal degeneration with retinal thinning is observed clinically and in histology, and in an attempt of self-repair RPE demarcation lines with fibrotic subretinal tissue may be found at the central edge of the detachment (Figure 3A and B). These may comprise a successful attempt of stabilising the retina, but resemble at the same time the first step in spontaneous subretinal PVR development (Figure 3C).

Since retinal reattachment surgery aims at closing breaks it is dependent on the induction of local and controlled wound healing processes, for which cryoretinopexy, laser photocoagulation and scleral buckling have been used. They induce central RPE atrophy with proliferation of the RPE at the edges; moreover, accumulation of pigmented macrophages and glial cell proliferation are found, which form the chororetinal scar.^{43b} The amount of uveo-vascular barrier damage, resulting from any form of trauma, i.e.

coagulation, may add to that resulting from retinal detachment and be the most relevant iatrogenic risk factor for development of PVR.^{44,45}

Risk Factors

The balance between desired wound healing of retinal tears and excessive wound healing resulting in an uncontrolled growth of fibrotic tissue is based on local environmental factors which may enhance the risk of PVR development.

This risk is influenced by the age of RD, surgical technique, the use of pharmacologic adjuncts and preventive measures. In general, preoperative risk factors have to be differentiated from surgical management and the use of adjuvant therapy.³ Beyond surgical techniques, surgical experience and skills,⁴⁶ the amount of retinal coagulation⁴⁷ and the choice of vitreous tamponade may be critical.

As preoperative risk factors for primary PVR, large retinal tears, long duration of retinal detachment, vitreous hemorrhage (Figure 9), aphakia and choroidal detachment have been identified. It may be not the number and size of breaks, but the mechanical trauma leading to these breaks which makes break size a risk; the greater the tissue trauma, the more cytokines are released from damaged tissue into the periretinal space, the greater is the capillary damage with thrombocyte and erythrocyte evasion into the vitreous cavity and the larger is the breakdown of the blood retinal barrier. The levels of proinflammatory

cytokines, namely interleukin 1, 6 and 8 as well as tumor necrosis factor alpha (TNF- α) and interferon- γ (IFN- γ) have been found to be increased in PVR.⁴⁸ But interestingly, they seem not to be correlated to the severity of PVR.⁴⁹ Vitreous hemorrhage has been identified as a strong risk factor.^{50,18,51} Aphakia may be a risk factor for PVR development since blood-veval barrier damage from anterior segment may allow diffusion of cytokines posteriorly.⁵² Failed retinal reattachment surgery and long standing retinal detachment may be additional risk factors.^{53,50}



Figure 9: Retinal re-detachment in this eye developed 11 weeks after vitrectomy with removal of an exudative retinal detachment and extensive subretinal hemorrhage due to a choroidal neovascularization. The hemorrhage had broken through into the vitreous cavity. Horizontal retinal folding may be induced by an as yet not clearly delineated PVR at the central margin of the temporally visible scar centrally to the residual subretinal hemorrhage (right picture margin).



Postoperative PVR is most strongly associated with the preoperative presence of PVR of any grade, inflammation, vitreous hemorrhage, excessive cryotherapy or photocoagulation, incomplete vitrectomy, repeated surgery, loss of vitreous during external drainage of subretinal fluid, undetected breaks and postoperative choroidal detachment. The use of air and sulfohexafluorides may be of impact, if no or incomplete vitrectomy has been performed.^{54,53,44}

Independent of these, the intravitreal number of RPE cells and persisting damage of the blood-ocular barrier have been identified as relevant risk factors.⁵⁵

The role of the immune system in the pathogenesis of PVR remains uncertain. Antiretinal auto-antibodies have been described in the context of PVR development,⁵⁶ so that an autoimmune process in the pathobiology of PVR cannot be excluded. But evidence is lacking that such would be of primary relevance for clinical evolution of the disease. Systemic steroid and immunosuppressive therapy may thus theoretically be supportive in the prevention and treatment of PVR, but have not soundly shown a disease modifying effect in a clinical setting.^{34,57,32,58,59}

Taken together, tissue trauma inducing retinal detachment, tissue trauma secondary to retinal ischemia, and tissue trauma due

to retinal detachment repair will result in a blood ocular barrier break down. This is rather closely correlated to the severity of PVR, and significant vitreous hemorrhage at the end of complete blood retinal barrier break down may be the strongest risk factor for PVR induction. In consequence of blood-retinal barrier breakdown, inflammatory cells and stimulating factors, i.e. cytokines and growth factors are released into the vitreous cavity.^{60,35,61,33}

Incidence and Timely Dynamics

PVR is generally expected to occur with an incidence of between 7 and 10% of uncomplicated rhegmatogenous retinal detachments,¹⁵ but has been reported in more than 25% in other series.⁶² Once the underlying reason is not uncomplicated retinal detachment, the risk may climb up to 40% in retinal detachment complicated by vitreous hemorrhage, postoperative inflammation, giant retinal tears and in posttraumatic retinal detachment.^{63,4} It has been assumed, that with an improvement in surgical techniques, the risk and incidence of PVR development would decrease over time, which has not unequivocally been proven.^{64,62} Most of the more recent clinical studies report incidences ranging from 5.1 - 11.7%.^{52,5}



Since none of the recognized risk factors correlates with the development or severity of PVR,⁵² the timely relation between the development of retinal detachment and its repair may be an important issue.⁶⁵ This has, however, so far not prospectively been evaluated in a clinical setting.^{66,67,62,68} The process of PVR formation is initiated by the trauma resulting from retinal detachment.²² This makes the identification and application of prophylactic and preventive strategies challenging.

Surgical Treatment

In general, surgery for PVR aims at stable reattachment of the retina, which is not different from the aim of conventional primary retinal reattachment surgery, in that most efforts have to be put into closing breaks and to release vitreoretinal traction.^{47,69} Nevertheless, these aims are much more difficult to achieve in cases of PVR. It may be challenging, to completely relieve vitreoretinal traction. For this, peeling of all periretinal fibrovascular membrane tissue and resection of the vitreous base as far as possible has to be achieved. This is usually complicated by a poor visualisation of the outer retina and vitreous base. Nevertheless, the success rate of surgical intervention for these cases has remarkably improved with the technologic evolution in vitreoretinal surgery, namely the routine use of vitrectomy techniques to relax vitreoretinal forces and the advent of silicone oil and perfluorooctane tamponades in not evidently stable retinal situations.^{70,71}

In moderate PVR, scleral depression using a local buckle or encircling band may allow the relaxation of vitreoretinal traction, e.g. circumferential traction caused by constriction of the vitreous base.¹⁹ The combination of scleral buckling and silicone oil tamponade may fail, namely in vitreoretinal pathologies of the inferior half of the eye, because the retina is - especially at the posterior buckle wall - not strongly depressed due to surface tension of silicone oil. It has therefore to be reinforced, that a mild to moderate buckle prominence is to be attempted to optimally relieve vitreoretinal traction in the lower circumference of the eye in combination with silicone oil.

In the recent few years, vitreoretinal strategy is tending away from buckling of any vitreoretinal pathology and in favour of vitrectomy techniques including relaxing retinotomies and retinectomies in combination with the use of endolaser and long-term or permanent retinal tamponades, namely in pseudophacic eyes.^{72,73} The major advantage of primary vitrectomy without scleral buckling may be that this procedure is less traumatising. Anatomical outcomes may be comparable, there is currently no evidence that the functional outcome might be improved.⁷⁴ It may though seem likely that better outcomes with regard to the binocular function can be achieved due to less extraocular trauma possibly affecting extraocular muscle function. Vitrectomy may be indicated in cases with no evident retinal breaks, where retinal traction and membranes presumably are the major cause for retinal detachment.^{47,75}



In severe PVR, vitrectomy is clearly the surgical technique of choice, including membrane peeling, vitreous replacement techniques and retinotomy or retinectomy, depending on the individual anatomical situation.²¹ In complex cases, combined lensectomy and vitrectomy might be considered.⁷⁶ Since PVR is a biologic process, which will proceed even after successful reattachment surgery, usually running 4 - 6 months or more after its initiation before quietening down (Figure 10), these dynamics have to be anticipated for the choice of the optimal tamponade and the timing of tamponade removal besides the local tolerability of the tamponade.^{70,77} The choice of tamponade and the decision for the timing of its removal are widely based on surgical experience and may be the crucial point determining success or failure in advanced cases of PVR.^{78,79,71} The use of the more recently introduced heavy silicone oils for PVR located in the inferior half of the retina may be limited by the fact that these have to be removed after two to three months due to their much faster emulsification as compared to pure silicone oils of 5000 centistokes density and their obviously higher complication, but not success rates.^{80,81,82} In more complex situations with circumferential traction, their sequential use with resolution primarily of inferior and secondarily of superior traction may be an option.⁸³

If stable retinal reattachment cannot be achieved, relaxing retinotomies or retinectomy may become necessary and, at least in experienced hands, allow excellent functional outcomes.^{84,85,86} This may namely be important if not all periretinal fibrotic tissue can be removed and the residual traction at the end of surgery is expected to lead to retinal redetachment, or if the biological activity of immature periretinal membrane tissue has to be expected to progress and to induce break reopening and retinal redetachment.⁸⁷ If not all traction is relieved until the placement of the tamponade, this may evade into the subretinal space during surgery or in the postoperative period, its complete removal usually being challenging. Therefore, tamponade placement should only be considered after all retinal traction is alleviated and, optimally, the edges of retinotomies and retinectomies have been sealed by photo- or cryocoagulation.

In advanced PVR, re proliferation has to be expected in two thirds of cases. If it involves the macular region, functional outcome is usually poor. Even if not quantifiable on the basis of visual acuity findings, patient satisfaction due to a subjective gain in visual function is surprisingly high in most instances despite several surgeries for the stabilisation of the retina.^{88,89} This may justify the significantly increased costs associated with the treatment of PVR.⁹⁰

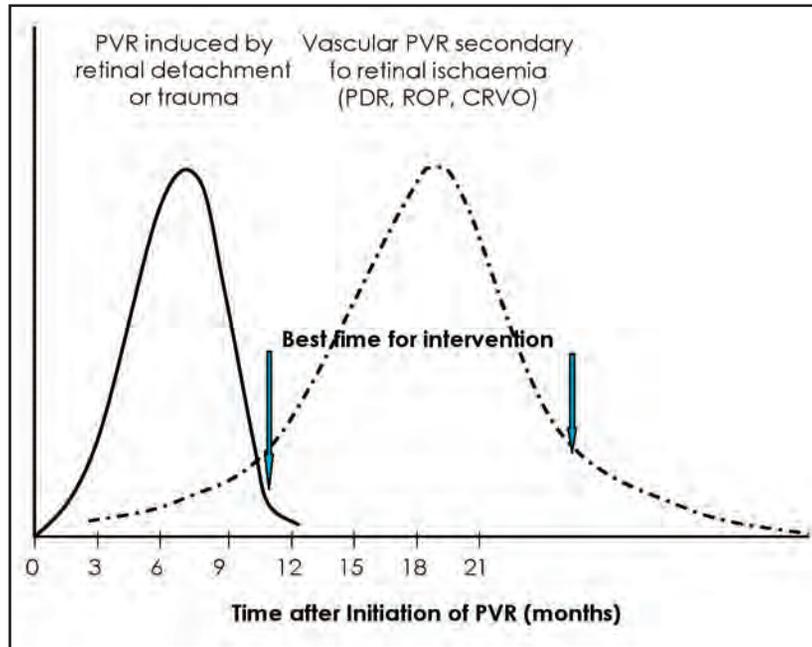


Figure 10: The time of the inducing event leading to PVR may be approximated for trauma and retinal detachment (closed line), but not so in chronic ischemic retinopathies (interrupted line). If the morphological situation is stable, the optimal timing for surgery for PVR may be after maturation of membranes and quietening down of fibroblastic activity. At this stage, the adherence of a PVR membrane may be stronger, but surgical delamination of the membrane from the retina may be facilitated because of a better demarcation and visibility of membrane extension. Since this is - in most instances due to an involvement of the macula or a worsening of surgical prognosis - merely not possible, multiple vitreoretinal surgeries have to be accepted as the price for a satisfying morphological, and in lucky instances, also better functional outcome. The timely dynamics of PVR are shorter after trauma and retinal detachment, and may be as long as several years in stable chronic ischemia such as late onset retinopathy of prematurity (ROP) and in the context of central retinal vein occlusion (CRVO), and usually somewhat in between in proliferative diabetic retinopathy (PDR). In the latter two instances, the impact of laser photocoagulation on PVR progression is hardly predictable. Obviously, the use of anti-VEGF therapeutics will remarkably enhance the process of fibrotic changes in vascular proliferations, thereby remarkably speeding up retinal traction development in proliferative retinopathies. Therefore, vitrectomy might be scheduled after ten to maximally twenty days after anti-VEGF therapy, and early intervention is strongly advised if tractional retinal detachment occurs,



A typical location of recurrent severe PVR is at the anterior part of the retina towards the pars plana, inducing cyclodialysis, hypotony and pupil distortion, and is usually associated with a poor prognosis.⁹¹ This specific entity of anterior PVR is most difficult to treat. Such is usually not possible without removal of the lens together with all capsular material and peeling off of membranes from the ciliary body and pars plana under indentation. Not surprisingly, corneal decompensation may be the consequence.⁹² If extensive retinotomies have to be performed, the risk of new induction of PVR leading to redetachment with macular involvement may be as high as 30%, resulting in poor to very poor visual outcome.^{93,94,95,48} This has found repercussion in the context of macular translocation surgery using 360° retinotomies.⁹⁶

Intra- and Peroperative Adjuvative Medical Treatment

Based on the above mentioned pathophysiological considerations, one might imagine several points, where adjuvant therapy for the treatment of PVR might help. We have learned that retinal detachment induces a process within the retinal tissue that goes far beyond wound healing and attempts a remodelling of the neuroretina. All strategies to control and direct wound healing and PVR have thus to be weighted against the potential benefits of retinal remodelling. The functional impact of biologic remodelling has not been profoundly addressed and remains

uncertain, but there is some indication, that retinal remodelling may partially protect the neuroretina and limit photoreceptor degeneration.

Obviously, individual pre-existing risks such as wound healing genetics or the presence of vitreous hemorrhage in the context of retinal detachment cannot be influenced. Beyond the points of influence, most and earliest efforts have been made to control the blood-retinal barrier breakdown and the inflammatory response in the context of PVR development by use of steroids. Interestingly, despite the absence of any clinical evidence and despite potentially severe side effects in the established doses, systemic as well as local, i.e. intravitreal steroids have been used by many vitreoretinal surgeons in the last decades.^{34,58,97,98,99,59} Antiproliferative agents have widely been evaluated, but have a limitation in the high sensitivity of the neuroretina to their dose-dependent toxicity. A number of studies have been undertaken to show the benefit of a variety of pharmacological interventions, including retinoic acid,^{100,101} dexamethasone,¹⁰² colchicine,¹⁰³ taxol, ¹⁰³ daunorubicin^{104,105} and multiple other antimetabolites,^{106,107} and also heparinoids,¹⁰⁸ have been evaluated alone or in combination in the last decades. Most of these agents have not achieved a level to justify their introduction into clinical evaluation, and none of them have reached entrance into clinical routine use.¹⁰⁹ More recently, growth factors and anti-inflammatory biologically active agents have been applied in order to control PVR.^{110,111,112,113}



Controlling the local biological environment has already been translated into therapeutic application,^{114,115,116,117,118,119,120} but the potential of interfering with the biological equilibrium in a clinical setting is as yet not predictable. Therefore, the way to their clinical application may as yet be long. Targeting chronic ischemia has not systematically been addressed but ascorbic acid has been applied in physiological concentrations *in vitro* in order to re-constitute the environmental situation in the vitreous after retinal detachment.¹²¹ More recently, evidence has been reported that statins may have therapeutic potential in the prevention of posterior vitreal detachment and inhibit the progression of PVR.^{122,123} Further work will thus have to go on in search of the optimal adjunctive treatment, which may be a combination treatment for the management of PVR.^{63,124,125}

With respect to adjunctive treatment, selection of the cases that would benefit from such treatment has remained an unsolved problem.¹²⁵ The evolution of drug delivery systems may carry a currently not predictable beneficial potential in the next future for successful prevention of proliferation and re proliferation after surgery for PVR,^{58,5} but its clinical suitability namely in the combination with the different tamponades has as yet not been assessed.

In conclusion, basing on current knowledge, preventive strategies remain a keystone for success, beyond these in the first place surgical experience¹²⁶ and strategies to minimize surgical trauma.^{69,20}

Summary and Perspective

The anatomical success after treatment of PVR has improved remarkably within the last decades, namely with introduction of vitrectomy and the use of silicone oil tamponade, which contrasts with a sometimes surprisingly poor functional outcome. This may be related to the induction of biological cicatrising and remodelling processes in consequence of separation of the neuroretina from the retinal pigment epithelium, which may proceed even after successful reattachment of the retina. Therefore a more profound pathophysiological understanding of the biological and biochemical processes involved and a preoperative recognition of cases at risk has to be reinforced in order to allow selection of eyes which take advantage from a primary prophylaxis of PVR at the time of or prior to retinal reattachment surgery. In cases where the development of PVR cannot be prevented successfully, a sustained drug delivery and the introduction of therapies influencing the biological cicatrising process carries promising potential and may realistically be expected within the next 5 to 10 years. Technical evolution has grown to such a high level that the keystone of technical success nowadays is surgical experience, but microrobotic systems to remove existing vitreoretinal adhesions and epiretinal membranes and apply drugs are under development,^{127,128} which may further improve the anatomical outcomes. After introduction of chromovitrectomy¹²⁹ including the use of triamcinolone to improve the visualisation of residual



vitreous cortex and epiretinal membranes,¹³⁰ the next step to improve the completeness of vitrectomy, which is a hallmark of surgical success, may be achieved by enzymatic vitreolysis, which is already on a good way and close to routine clinical application.¹³¹ A reconstitution of the properties of the vitreoretinal environment, namely a rebalancing of cytokines and growth factors after occurrence of retinal redetachment may be an option at the horizon of preventive strategies. A better understanding of the factors controlling PVR and visual outcome will remain important fields of clinical research in PVR.

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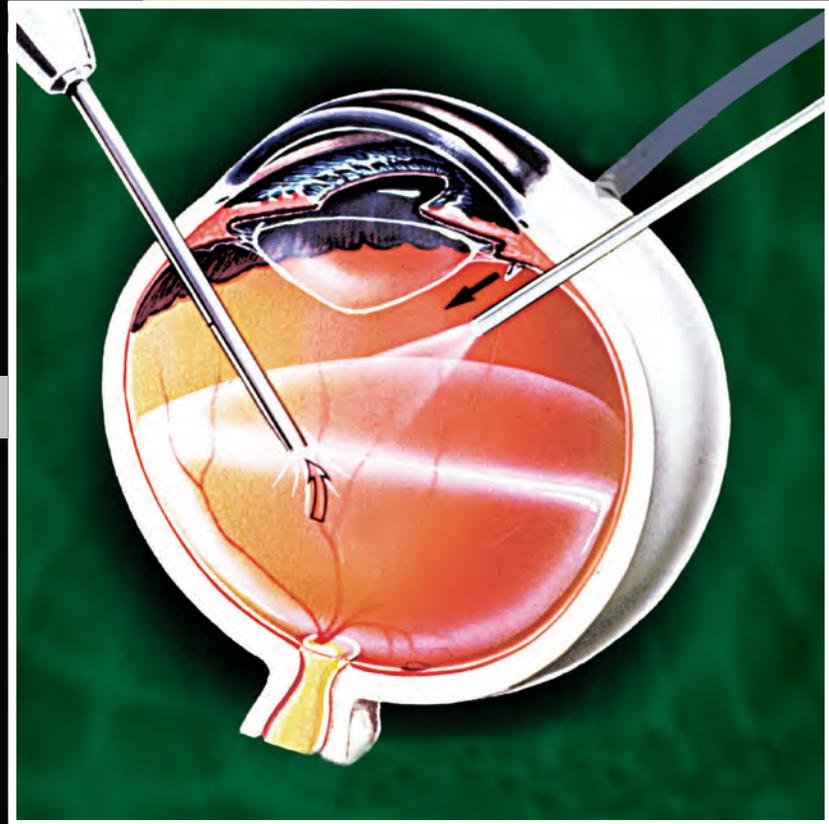
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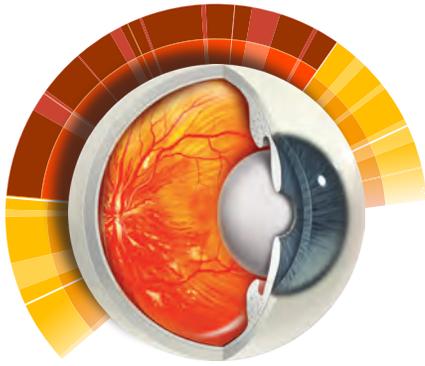


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Section 7

Vitrectomy Techniques and Technology



26

Anterior Vitrectomy

SAMUEL BOYD, MD

Anterior vitrectomy is a crucial tool in the skill set of the anterior segment surgeon. Although a planned anterior vitrectomy may be performed in such settings as traumatic cataract removal or secondary IOL placement, this procedure is most often an unplanned—and unwelcome—addition to a cataract surgery. Even the most experienced surgeon will occasionally be inadvertently faced with vitreous prolapsing into the anterior segment. Thus, a surgeon's comfort with basic anterior vitrectomy principles and techniques can defuse intraoperative stress and improve patient outcomes when complications involving the vitreous occur.¹

During cataract surgery, it is imperative to quickly recognize complications such as

posterior capsular tear with associated vitreous loss. One must attempt to maintain a controlled working environment while avoiding subsequent problems, including hypotony and vitreoretinal traction.

The main goals of anterior vitrectomy are to free the anterior segment of vitreous and to release any vitreous traction, which may cause breaks or tears in the retina (Figure 1). Important matters to consider when performing anterior vitrectomy include the accessibility of vitreous and retained lenticular tissue, minimization of secondary complications, and optimization of visual and surgical outcomes.

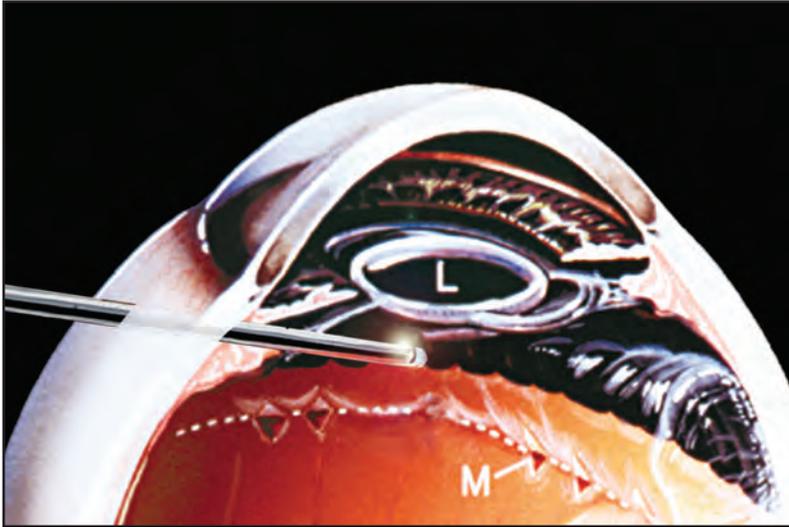


Figure 1: Anterior vitrectomy. Through a pars plana approach (3mm). An anterior vitrectomy is performed to release traction over peripheral retinal tears (M). Intraocular lens (L). (Art from Jaypee - Highlights Medical Publishers).

Vitreous Anatomy

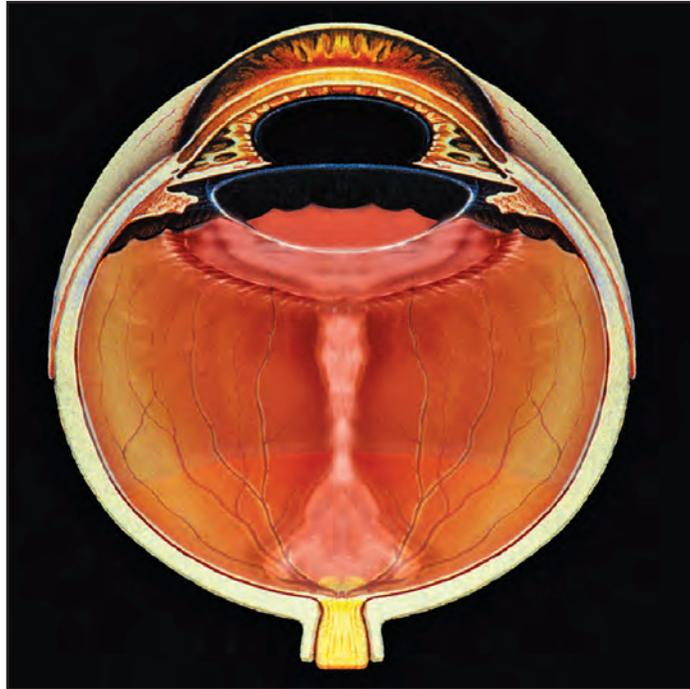
A basic knowledge of vitreous anatomy is helpful for understanding the intraoperative behavior of the vitreous. While the vitreous is 98 to 99 percent water, it also contains a network of fine collagen bundles suspended in coils of mucopolysaccharide hyaluronic acid. These collagen and hyaluronate components impart a gel-like consistency and a degree of elasticity to the vitreous. While a small amount of traction can be absorbed by the vitreous, a larger amount may be transferred through its collagen bundles to the posterior and peripheral retina, resulting in retinal tears and macular edema.² The vitreous adheres most firmly to the retina at the optic nerve and at the vitreous base. It extends approximately 2 millimeters anterior and 4 mm posterior to

the ora serrata. Looser attachments also occur along the retinal vessels, in the perimacular region and in the periphery of the posterior lens capsule (Figure 2).

The Role of Vitrectomy in Anterior Segment Surgery

Vitrectomy is a word the anterior segment surgeons really do not want to say nor hear. It conjures certain complications as capsule rupture, falling lens fragments, anterior chamber IOLs, surgically induced astigmatism, cystoid macular edema and retinal detachment. However, surgeons can be taught to do better. There are definite indications for vitrectomy, and proper performance can rescue surgical results. Advances in techniques and technology

Figure 2: The gel in the vitreous chamber is stagnant, unlike the fluid in the aqueous humor, which is replenished continuously. For this reason, when cells, blood, or other inflammation by-products get in to the vitreous, they remain there until surgically removed. A network of collagen and the negative charge of hyaluronic acid supports the water. The water content of the lens is around 75%, less than that of the vitreous, at 98%. Still, the viscosity of the vitreous is about 2-4 times more than pure water, which is why it has the consistency that it does. For reasons still unknown, around the age of 50 the vitreous begins to lose hyaluronic acid, resulting in quicker changes to an increasingly watery consistency. (Art from Jaypee - Highlights Medical Publishers).



mean that vitrectomy no longer has to be a dirty word, or a daunting procedure.³

Lens extraction performed through two paracentesis-type incisions offers unique advantages that enhance surgical control and safety (Figure 3). The crucial difference is not the size of the incisions; it is the separation of inflow and outflow. This same separation of inflow and outflow facilitates the perfor-

mance of anterior vitrectomy, for the reasons mentioned above.

Bimanual phaco also provides significant advantages in the management of complications. If the posterior capsule is compromised during surgery, the first goal of the surgeon is to maintain stability of the anterior chamber to prevent both posterior migration of lens material and anterior prolapse of the vitreous.⁴

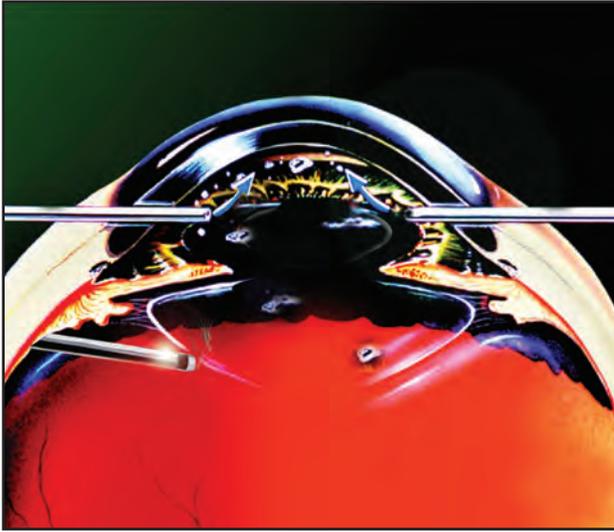


Figure 3: Bimanual Anterior Vitrectomy. A self-retaining irrigating cannula is placed through a limbal paracentesis and is angled toward the pupil. The sleeveless vitrectomy shaft is inserted through the pars plana sclerotomy until the tip can be visualized in the retro-pupillary space. If it does not pass through the incision easily, it is important to slightly enlarge the opening rather than to force the entry. Using low flow and vacuum settings, and as high a cutting rate as possible to minimize vitreous traction, a thorough anterior vitrectomy is performed. One should focus posteriorly enough with the microscope to keep the tip under direct visualization at all times. One should attempt to keep the vitrectomy tip behind the pupil if possible. While any transpupillary bands of vitreous will still be severed, this will avoid removing the dispersive viscoelastic that fills the anterior chamber. (Art from Jaypee - Highlights Medical Publishers).

By maintaining infusion in the anterior chamber, it becomes safer to use the phaco needle, aspiration tip or vitrector to remove residual lens tissue. Irrigation should never be brought down into the capsule or vitreous space, where it may dislodge lens tissue, enlarge the capsular tear or engage the vitreous.

Advantages

Pars plana anterior vitrectomy has several advantages compared with current methods for dealing with vitreous loss. Anterior vitrectomy employs continuous infusion and aspiration through the same instrument and incision. This circumstance may cause further vitreous prolapse toward the incision.⁴ The cutter is

usually used at a slow rate with a large aspiration port, which can hydrate the vitreous and exert greater traction on the peripheral vitreous and retina.⁵

Complete vitreous removal from the anterior chamber may be difficult due to fluid flowing out of the wound and limited accessibility.

With a pars plana lensectomy, the pars plana incision can be placed in a position that offers optimal access to the remaining lenticular material. By allowing the surgeon to pull down prolapsed vitreous from the anterior chamber, the posterior approach can reduce the amount of vitreous removed overall (Figure 4). Removing less vitreous from the eye may lower the likelihood of postoperative hypotony.

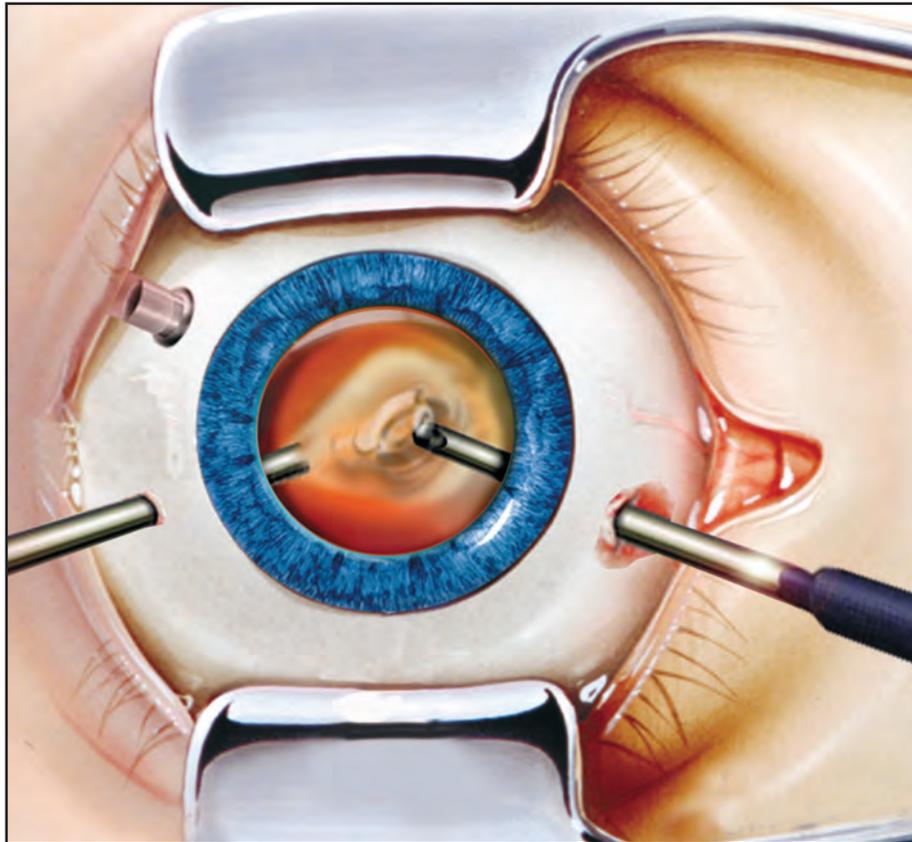


Figure 4: Lens extraction (Lensectomy) through pars plana approach at 3mm sclero-limbal. (Art from Jaypee - Highlights Medical Publishers).

In addition, a pars plana approach facilitates the removal of retained lenticular material near the posterior capsule, iris, and ciliary body and thus lessens the chance of secondary inflammation and cystoid macular edema.⁶

Because the procedure is performed in a closed chamber, reduced intraocular turbulence minimizes IOP fluctuations and lessens the risk of suprachoroidal hemorrhage. Furthermore, pars plana vitrectomy reduces corneal edema

that occurs secondary to trauma from anterior vitrectomy performed through a phaco incision. According to Chalam and Shah⁵ 96.5% of eyes studied achieved a BCVA \geq 20/40. Furthermore, 72.4% achieved a BCVA \geq 20/20 postoperatively at 3 months. Vitreous loss with posterior capsular rupture occurred in all eyes, and cystoid macular edema was noted in two (6.8%) eyes. These results compare favorably with those of cataract surgery in which no vitreous loss is noted or anterior vitrectomy is used for complicated cataract surgery.⁷



Pars Plana Anterior Vitrectomy

When nuclear remnants fall through a rent in the posterior capsule (but remain within the surgeon's view), or vitreous prolapses to the wound, then the phaco surgeon should consider pars plana vitrectomy. The advantage of this approach over vitrectomy through a corneal incision resides in the fact that the vitreous gel is pulled in a posterior direction by the vacuum, thus limiting vitreous loss, preventing incarceration of vitreous strands in the incision and facilitating a thorough clean-up of the anterior segment.

For vitreous removal, the cut rate should be set high, at 500 to 600 cpm, with low to moderate aspiration. A high cut speed for vitreous removal causes vitreous to flow continuously into the cutter, resulting in less pulsatile stress being placed on the retina.⁸ The vitrector is then placed through the capsular tear just below the capsule with the aspiration port facing up toward the cornea. The cutter should be maintained in a fairly central position and not moved peripherally beyond the plane of the iris root to avoid undue stress on the vitreous base. The vitreous is removed to a level just posterior to the capsule (Figure 4).

23G / 25 Gauge Vitrectomy System

To perform a pars plana vitrectomy with 23G / 25-gauge instrumentation, irrigation is maintained in the anterior chamber with reduced pressure (lowered bottle height) as a stab incision is made with an MVR blade or other suitable instrument 4 mm posterior to the limbus, usually in the superotemporal or inferotemporal quadrants. The conjunctiva is pushed to one side so that intact conjunctiva will cover the sutureless incision afterwards (Figure 5). A small-gauge, high speed cutter is introduced and the lens fragments removed.⁹ Irrigation is titrated to maintain a stable anterior chamber.

According to David Chang, M.D., in many cases it is recommended to perform bimanual anterior vitrectomy with a separate limbal side-port infusion and high cutting rate through the use of pars plana sclerotomy for the vitrectomy cutter.

Following vitrectomy, irrigation is maintained while cortical remnants are aspirated and the capsule cleaned as necessary. Finally, a cohesive viscoelastic is introduced through a corneal incision while continuous irrigation is still maintained, preventing further vitreous prolapse.

Figure 5: 23G/25 G Vitrectomy. During surgery it is recommended to increase the IOP (ie. 35 mmHg) with vacuum up to 400 mmHg. When removing the micro cannulas, maintain the IOP at 20 mmHg. After plugging the cannulas remove them with a forceps, and then apply pressure over the sclerotomy to close the wound and prevent conjunctival hemorrhage. In paediatric cases it is recommended to suture the sclerotomies. The 23/25 gauge inserter provides a solid wire trocar mounted to a easy handle. The inserter comes with the 23/25 gauge cannula pre-installed and is delivered in a safe, retracted position.

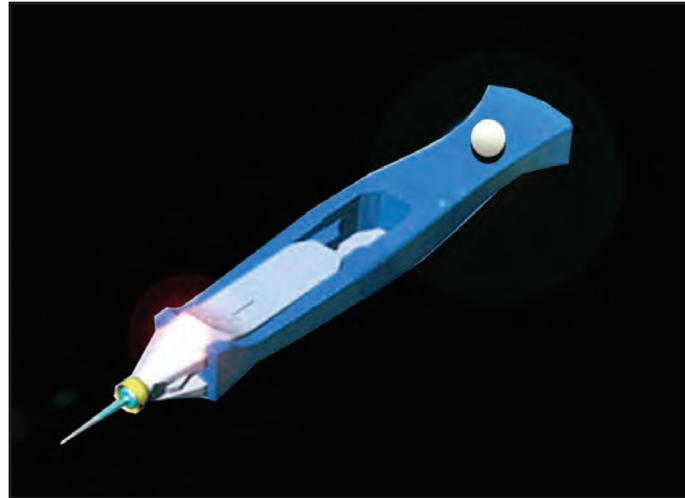
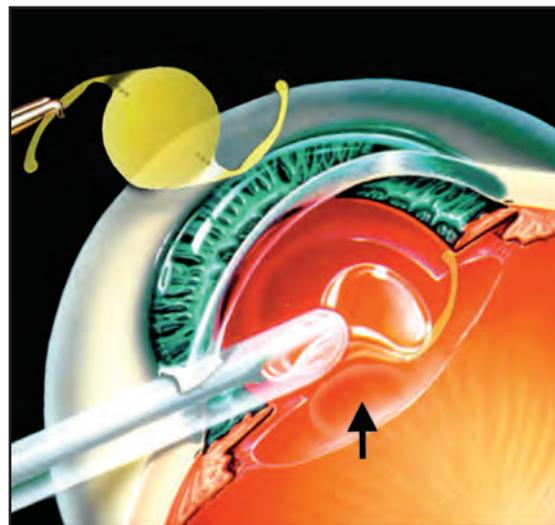


Figure 6: Intraocular foldable lens inserted and accommodated on the sulcus to avoid contact or risk with the anterior vitreous due posterior capsule rupture (arrow). (Art from Jaypee - Highlights Medical Publishers).



The haptics of the intraocular lens can then be inserted into the ciliary sulcus and the optic captured behind the capsulorrhexis to avoid any rupture of the posterior capsule (Figure 6).¹⁰

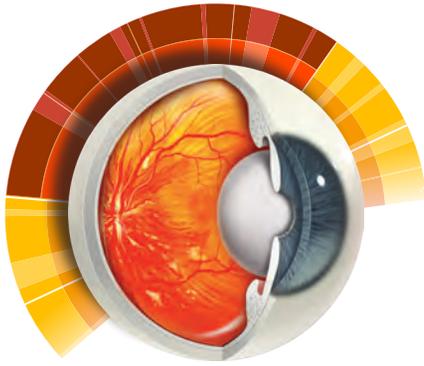
Following removal of viscoelastic with irrigation and aspiration, the surgeon should ensure a vitreous-free anterior chamber.

Converting a difficult situation into a familiar situation remains the goal of most approaches to challenging cataract cases. Pars plana vitrectomy and vitreous staining provide the anterior segment surgeon with valuable tools in a variety of cases. Adopting these relatively simple techniques will improve outcomes and allow greater flexibility in the operating room.



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27

Pars Plana Lensectomy

SAMUEL BOYD, MD

Vitreoretinal pathologies are serious conditions primarily affecting traumatized patients with an estimated overall prevalence of 0.14 percent in the Caucasian population.^{1,2} Pars plana lensectomy has been shown to be effective in achieving visual improvement during surgery.³ Since the first report of surgical repair through vitrectomy by Kelly and Wendel,⁴ several modifications of the original technique have been described. The modifications involve many unresolved controversies associated with vitreous surgery. These include the appropriate vitreous substitute used for intraocular tamponade,⁵⁻⁹ the optimal duration of intraocular tamponade and postoperative positioning,¹⁰⁻¹² the benefits of adjuvant therapy,¹³⁻²⁰ the role of internal limiting membrane (ILM) peeling, the optimal staining material,²¹⁻³⁰ and the extent of vitrectomy needed to achieve a successful surgery.³¹

Indications for Lensectomy

Pars plana lensectomy with an ultrasonic phacemulsifier system is one of the latest advances both in retinal surgery and cataract surgery. In cases of congenital cataracts and cataracts in young adults, the lensectomy can be the procedure of choice. Complications like after cataract, vitreous loss, bullous keratopathy, epithelial down growth, anterior synechiae, secondary glaucoma and wound dehiscence which are met with during conventional surgery, are either absent or seen in significantly small numbers, after pars plana lensectomy. Since this procedure utilizes a small scleral incision and a closed system to maintain intraocular pressure during the surgery, preoperative reduction of intraocular pressure is not necessary.³²



Early ambulation of the patient is possible since no corneo-scleral section has been made. The most important advantage of this procedure is that vitreous loss does not occur. Lensectomy can also be done in cases where vitrectomy or scleral buckling procedures are indicated in order to obtain a clear media, if the lens is cataractous (Figure 1).

Lensectomy and Anterior Vitrectomy in Pediatric Cataracts

Usually, the basic surgical techniques for pediatric cataract surgery have been lensectomy and anterior vitrectomy (LAV).³³⁻³⁸ These techniques provide a clear visual axis but needs rehabilitation of aphakia by the use of spectacles or contact lenses. The approaches

for LAV are either limbal or via pars plana (Figure 2). Most surgeons prefer limbal approach to minimize the risk of damaging the peripheral retina and to prevent vitreous from becoming incarcerated in the wound. This approach is particularly used for the management of pediatric cataracts associated with uveitis.

With the general acceptance and the advances in design of intraocular lenses as a mode of aphakic correction especially in children (older than 2 years of age), LAV is losing ground to modern cataract surgery techniques because it does not allow the option of placement of a posterior chamber IOL. Some authors have described a technique of pars plana lensectomy where a peripheral rim of anterior capsule is left intact for a sulcus fixation of the IOL (Figure 3).

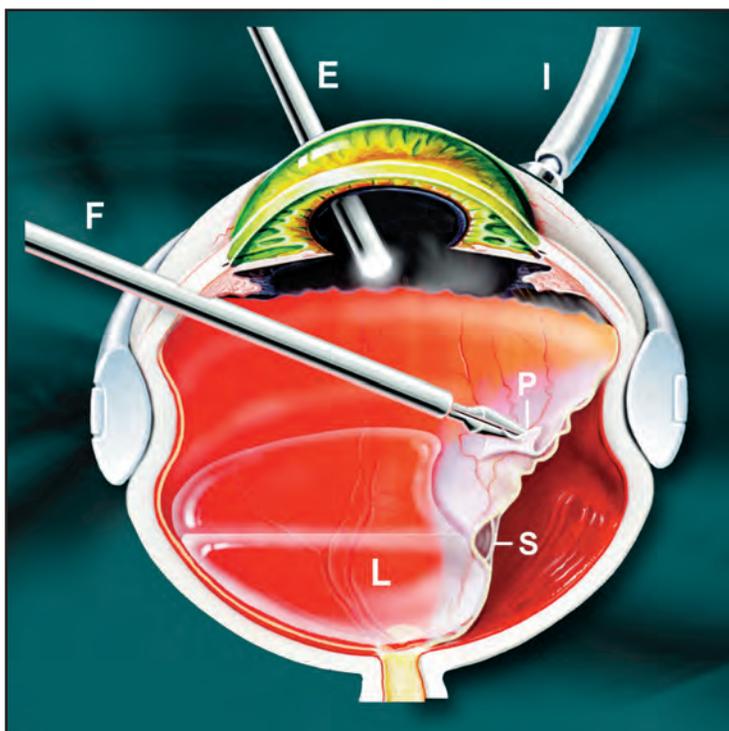


Figure 1: The central vitreous gel and lens are removed before injecting perfluorocarbon liquid (L). After the lens is removed, a total posterior vitrectomy is performed and a vitreoretinal pic or mini forceps (F) is used to remove any persistent traction from epiretinal membrane (P). Infusion cannula (I), Endoilluminator (E). (Art from Jaypee – Highlights Medical Publishers).

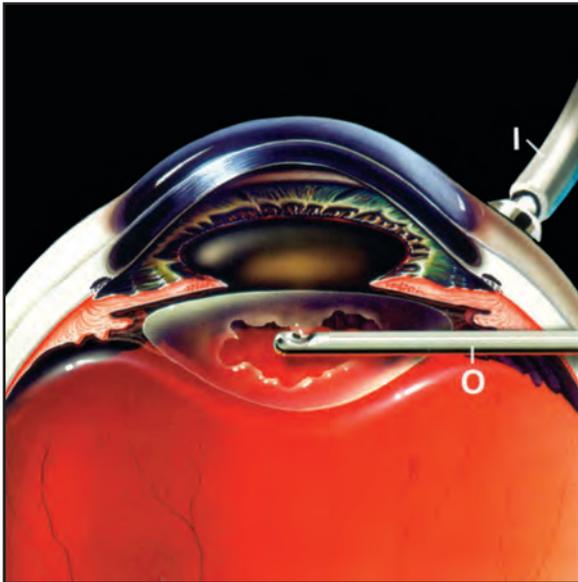


Figure 2: Combined Pars Plana Cataract Extraction and Vitrectomy – Removal of Nucleus and Cortex. In cases of pars plana vitrectomy requiring lens removal, the lens may be removed through the pars plana approach. A phacoemulsifier, aspirating cannula or vitreous cutter such as the Ocutome (O) shown, removes the nucleus and cortex. Infusion is supplied through a separate terminal (I), which will also be used during the vitrectomy stage of the operation. (Art from Jaypee – Highlights Medical Publishers).

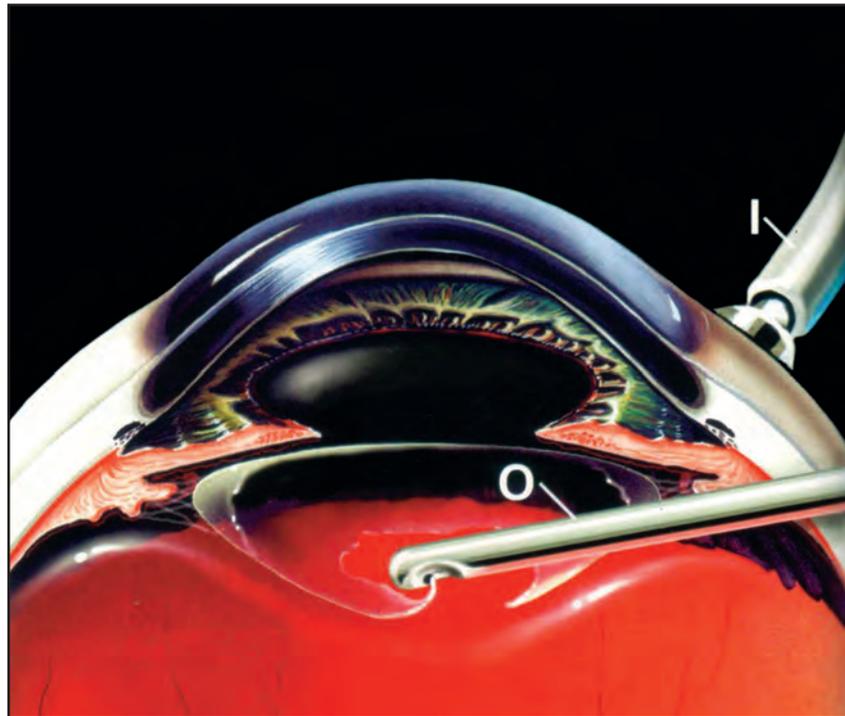


Figure 3: Combined Pars Plana Cataract Extraction and Vitrectomy – Removal of the Posterior Capsule. When planning to insert an intraocular lens, an adequate capsular support is preserved, if possible. Some surgeons prefer to remove the posterior capsule as shown, through the pars plana with the vitreous cutter (O). Following the pars plana vitrectomy, if a decision is then made to implant an intraocular lens, a limbal incision is performed and an intraocular lens is placed over the intact anterior lens capsule. Pars plana infusion terminal (I) is used for both the lensectomy and vitrectomy. (Art from Jaypee – Highlights Medical Publishers).



Surgical Procedure in Luxated Lens Material

This technique is preferred when there is a significant posterior capsular disruption, trauma, rupture or dislocation and vitreous prolapsed into the anterior chamber. The surgical goal is to remove the entire lens, prolapsed vitreous and, if required, to manage any posterior segment traumatic abnormality (vitreous hemorrhage, intraocular foreign body (IOFB), retinal detachment, etc., (Figure 4).

Pars plana lensectomy is of undoubted value in the older patient with a hard lens, which requires ultrasonic fragmentation before aspiration. Should posterior displacement of lens matter occur, it allows easy access to the vitreous cavity. The goal is to remove the entire lens, prolapsed vitreous, and in some cases to insert an intraocular lens. The procedure is as follows: Creation of three conjunctival dissections: inferotemporal, superotemporal and superonasal. Three sclerotomies at the same sites, 3.0 mm posterior to the limbus, with a MVR blade (in children under three years of age), the sclerotomies are created more anteriorly because the pars plana is not fully developed. A 4- or 6-mm infusion cannula is sutured in place into the inferotemporal sclerotomy. The infusion is not turned on until the cannula port is visualized in the vitreous cavity. The MVR blade is introduced through one of the sclerotomies and passed through the equator of the nucleus to judge central hardness. In children, or young adults, the lens can be removed with the cutting/aspiration probe.

In older individuals with harder lenses, the lens nucleus require ultrasonic fragmentation before irrigation and aspiration of the cortex and posterior capsule. Depression with a cotton-tipped applicator can aid in removal of peripheral lens material. Vitrectomy should be performed for removal of anterior prolapsed vitreous, significant vitreous opacity (usually blood), and retrieval of dropped lens fragments (Figure 5).

Posterior lens fragments are crushed between an endoillumination probe and the vitreous cutter, after the surrounding vitreous has been removed. Fragmentation is only performed in the anterior vitreous cavity after the lens fragments have been safely elevated off the retina. Only surgeons experienced in vitreoretinal techniques should attempt posterior vitrectomy. In absence of capsular support, a posterior scleral fixated posterior chamber IOL, a sulcus or anterior IOL also may be placed.

Anterior Vitrectomy

Most surgeons prefer to perform anterior vitrectomy along with primary posterior capsulorhexis to decrease the incidence of posterior capsule opacification.^{39,40} Anterior vitreous acts as a scaffold and helps in cellular migration and proliferation. The vitrectomy may be performed using limbal or pars plana route. In children the aim is to remove only central anterior vitreous in the posterior capsulotomy opening.⁴¹

Figure 4: Aspects of Two-Phase Rehabilitation of Penetrating Trauma. Phase 1 of rehabilitation of trauma, which is the acute stage, involves the primary objective of repairing the cornea (A). Phase 2 involves repairs to avoid the progression of several types of further damage. With a perforating injury, the choroid (C) may swell two to two and a half times its normal thickness. This will push the vitreous (V) forward (blue arrow) which will in turn push lens (L) and iris (I) forward (red arrow). Fibrin will begin to be laid down in nature's attempt to repair the wound, causing adhesions to form between the iris, lens and / or vitreous material, and the cornea. Peripheral anterior synechiae (S) formation and secondary angle closure glaucoma may also result. (Art from Jaypee - Highlights Medical Publishers).

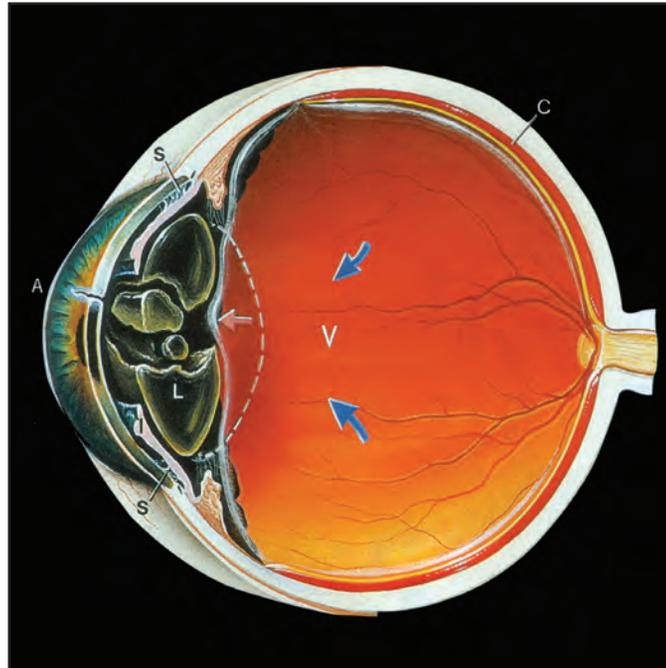
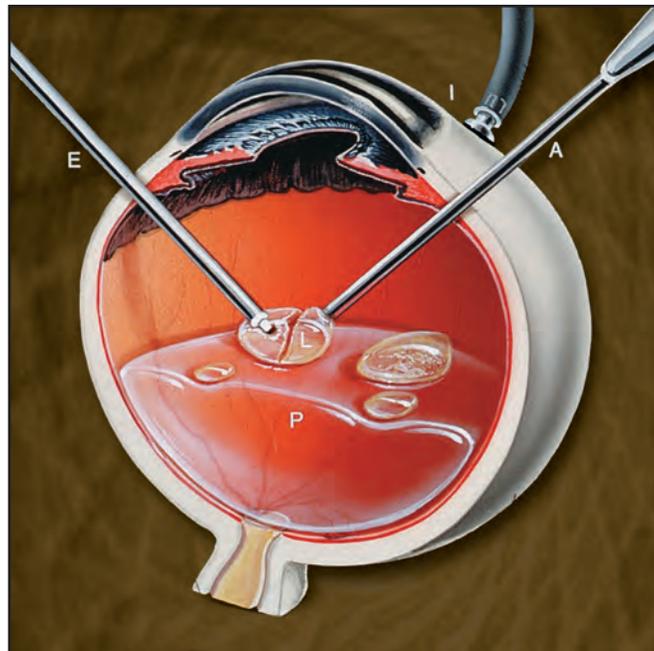


Figure 5: Use of Perfluorocarbon Liquid for Dislocated Lens Removal - Initial Stages. The surgical technique involves a three-port pars plana vitrectomy with removal of as much as possible of the base of the vitreous gel prior to removal of the lens. After the vitreous has been removed, perfluorocarbon liquid is injected over the optic nerve head to float the dislocated lens off the retina and into the anterior vitreous cavity. The dislocated lens is then fragmented. Perfluorocarbon liquid (P). Lens Fragments (L). Phacofragmentation tip (A). Tissue manipulator (cannula with endoilluminator) (E). Infusion cannula (I). (Art from Jaypee - Highlights Medical Publishers).





Lensectomy in Diabetics

In diabetic patients with proliferative retinopathy, lensectomy may improve intraoperative visualization or help to gain access to peripheral fibrovascular plaques. According to Dean Elliott, MD from the Kresge Eye Institute at Wayne State University in Detroit, eyes that underwent lensectomy had less postoperative rubeosis than eyes that remained phakic. Eyes that underwent lensectomy typically had more advanced disease; however, they were able to receive more thorough treatment and actually had a lower incidence of postoperative rubeosis.⁴²

These can be explained since lensectomy enables more complete removal of anterior vitreous and membranes. After lensectomy, usually you are able to perform careful scleral depression, dissect the vitreous base, and use endolaser and/or the laser-indirect ophthalmoscope to perform thorough photocoagulation from the arcades to the ora serrata.

Complications

The most common intraoperative complications are vitreous hemorrhages and small lens dropping falling into the vitreous cavity. Some of these are usually retrieved after careful vitrectomy.⁴³ Accidental sphincterectomy may also occur with the cutter probe, but this did not cause any significant optical or cosmetic problems. Iritis and transient glaucoma may be presented in the postoperative period.

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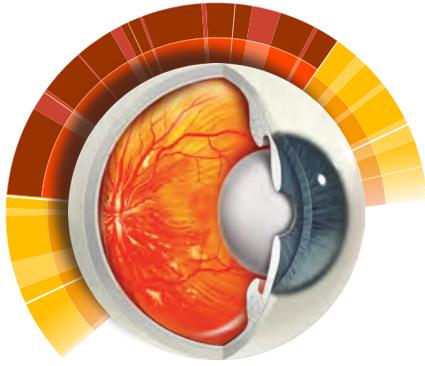
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Retinectomies and Retinotomies

JANICE C. LAW, MD.,
JIONG YAN, MD.,
PAUL STERNBERG JR., MD.

Introduction

Retinectomies (excision of the retina) and retinotomies (full thickness incision of the retina) can be generically classified into two main functions in vitreoretinal surgery: (1) access to the subretinal space and (2) relaxing contracted retina. Access retinotomies are frequently used to drain subretinal fluid (drainage retinotomy) from the subretinal space. They can be conveniently used to reach the subretinal space for removal of subretinal fibrosis bands or a choroidal neovascular membrane.

Subretinal membranes in proliferative vitreoretinopathy can take the form of a band, a sheet, or napkin ring configuration. Retinal detachments with PVR will fail to attach due to these subretinal membranes if they are not removed or relaxed. Small access retinotomies must be made to remove subretinal bands if it exerts significant traction. In the case of a subretinal sheet or napkin ring, the creation of a more extensive retinotomy or retinectomy, with the retina folded back on itself may be required to expose the membranes for careful

dissection away from the undersurface of the retina or attachments to the RPE.

Certain complex retinal detachments require relaxing-type retinotomy and/or retinectomy to achieve a satisfactory reattachment. In the event of retinal incarceration or retinal contraction from fibrous proliferation, a relaxing retinotomy or retinectomy is often attempted as a last resort to relieve the retinal traction after other methods, such as scleral buckling and vitrectomy with peeling of epi- and sub-retinal membranes, have failed. This technique was first reported by Machemer and colleagues in a case of retinal incarceration in a traumatic scleral wound.^{1,2} Zivojnovic et al described the use of relaxing retinotomy to relieve severe retinal traction in cases of non-traumatic fibrous proliferation.^{3,4} Parke and Aaberg further expanded the role of retinotomy in proliferative vitreoretinopathy (PVR).^{5,6} When considering such a procedure, the benefit of preserving the posterior pole should be weighed against the loss of the peripheral retinal function through a retinotomy. The size of a retinotomy may vary from a small defect to drain subretinal fluid to 360° excision of the peripheral retina. In



this chapter, we will review the indications, surgical techniques and complications of relaxing retinectomy and retinotomy in the setting of retinal detachment repair.

Indications

Proliferative vitreoretinopathy (PVR)

- Focal starfold
- Diffuse contraction
- Circumferential contraction
- Anterior retinal displacement
- Giant retinal tear
- Subretinal membranes

Proliferative vascular retinopathy/Proliferative diabetic retinopathy

- Longstanding fibrovascular proliferation
- Anterior hyaloidal fibrovascular proliferation

Retinal incarceration

- Penetrating trauma
- Surgical sclerotomy site

Pathogenesis

PVR is the leading cause of failure in retinal detachment surgery. Retinal pigment epithelial (RPE) cells that are liberated at the time of the original retinal detachment or at the time of repair are considered to be responsible for the occurrence of PVR.^{7,8} The RPE cells presumably undergo fibroblastic proliferation and transform into tissue macrophages. With the ability to mature into fibrocytes, synthesize collagen and produce a membrane, they create vitreal-retinal contraction and eventually lead to retinal detachment.^{9,10} Despite aggressive membrane dissection, severe retinal foreshortening prevents adequate retinal reattachment to the underlying RPE layer.

In contrast, in traumatic or surgical retinal detachment with retinal incarceration, true retinal foreshortening occurs due to loss of retinal tissue. In addition, fibrous proliferation at the site of injury may further exacerbate the contraction and retinal foreshortening.

Surgical Procedures

When encountering retinal detachment with traction, the decision whether to perform a retinectomy or to place a scleral buckle alone is made at the time of surgery. An inability to flatten the retina during air-fluid exchange after careful membrane dissection indicates the need for a relaxing retinotomy or retinectomy. The location and severity of the traction are important factors to consider in making operating decisions.

Since most traction can be relieved or minimized using a scleral buckle, it is recommended that the eye be encircled with a scleral buckle at the time of retinectomy. Michels et al reported that scleral buckling reduces the vector force exerted by the epiretinal membrane on the retina, thereby reducing traction.¹¹ The contraction of the epiretinal membrane produces a vector force perpendicular to the vitreous base and pulls the retina away from the underlying RPE (Figure 1). When a scleral buckle is placed under an area of traction, it changes the shape of the eye wall from concave to convex. This change reverses the direction of the perpendicular vector force by the epiretinal membrane, shifting it back towards the underlying RPE.

Extensive membrane dissection is important in relieving the residual traction. Minimizing any residual fibrous membranes can decrease significantly the likelihood of

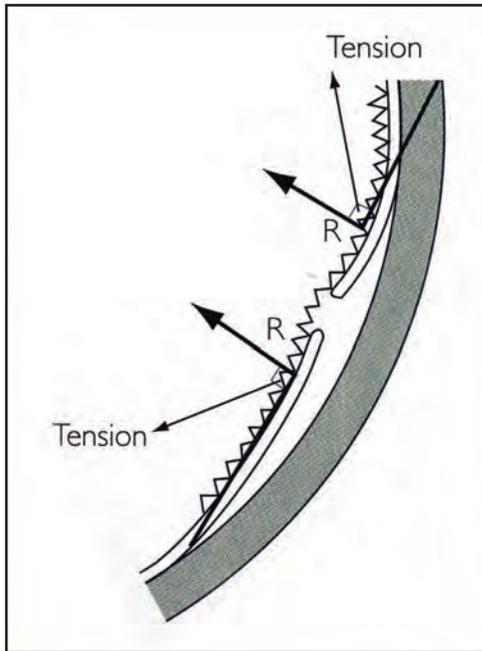


Figure 1: The contraction of an epiretinal membrane produces a perpendicular vector force towards the vitreous base and pulls the retina away from the underlying retinal pigment epithelium.

recurrent detachment. Posterior membranes are easier to remove due to better visualization and access, making posterior relaxing retinectomies or retinotomies rarely indicated. In special cases with persistence of fibrous traction despite scleral buckling and membrane dissection, retinectomies or retinotomies are needed to facilitate successful reattachment.

The location of a retinotomy may be anterior or rarely, posterior. A more anterior retinotomy has the advantages of preserving retinal function and minimizing significant hemorrhage. It is, however, technically more difficult. On the other hand, a posterior retinotomy is easier to perform, does not require lensectomy and usually allows satisfac-

tory reattachment anterior to the retinotomy site.

Perfluorocarbon liquids (PFCL) can be used as a diagnostic tool to assess areas of remaining traction thereby determining the need and extent of the retinotomy. In addition, the property of perfluorocarbon liquids (colorless, optical clarity, high density, and low viscosity) have given it popularity as a surgical adjunct or “third hand” during delicate delamination of membranes.

If the retina fails to flatten or if the PFCL moves subretinally after the initial retinotomy with the PFCL in the posterior retina, the retinotomy should be extended until the remaining retina reapposes to the underlying RPE. The retinal flattening should occur with PCFL rather than air or gas because the latter has a greater surface tension and provides tamponade for as long as it remains in the eye. An artifactually reapposed retina will detach once the air or gas absorbs.

The use of a wide-angle viewing system facilitates the visualization and assessment of the overall status of the anterior retina.¹² It allows the surgeon to determine the extent of the retinectomy needed and to ensure adequate relief of traction. The following clinical examples will address the different surgical techniques of retinotomies and retinectomies according to the indications.

PROLIFERATIVE VITREORETINOPATHY (PVR)

1. Focal Starfold (Figure 2)

After a 360° application of diathermy to the area of proliferation with extension to the

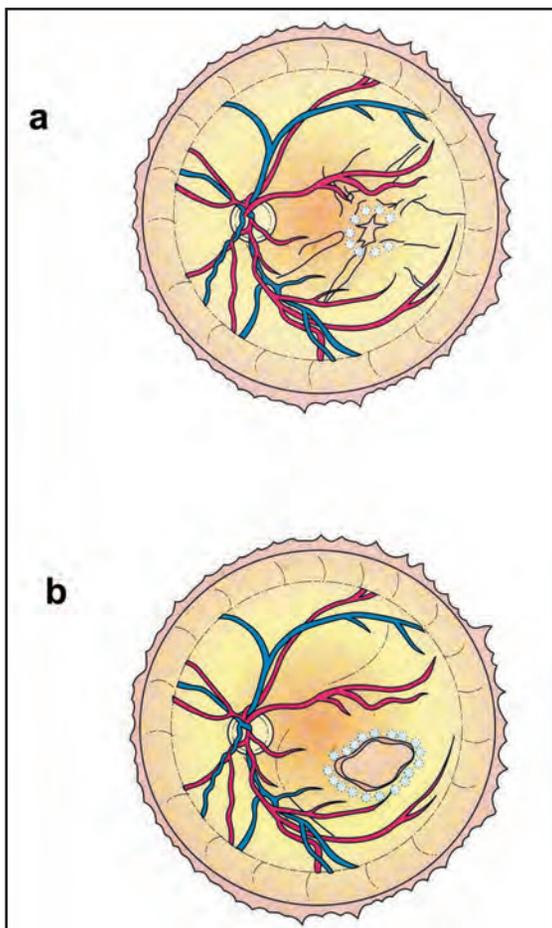


Figure 2: Focal Starfold. (a) Diathermy applied surrounding the center of proliferation. A retinotomy hole created. (b) Surrounding retina attached after removal of focal contraction. Endolaser applied to the edges of retinal defects.

surrounding normal retina, a retinotomy hole may be created using either the diathermy or an intraocular scissors. Care should be taken not to damage the underlying RPE and choriocapillaris by the diathermy or scissor tips in the area of closely apposed retina to the RPE. Significant intraocular hemorrhage may occur as a result. Following diathermy, an illuminated pick or scissors blade is used to enter the subretinal space in the area of

the greatest elevation. The retina is then elevated and separated away from the RPE before dissection. This may also be accomplished using the aspiration function of the vitrector, lifting the retina away from the underlying RPE before safely switching to cutting mode. In case of intraocular hemorrhage due to inadequate diathermy when cutting the retina, an illumination/coagulation or illumination/coagulation/suction (three-way tissue manipulator) instrument may be used to achieve hemostasis.

Following complete removal of the area of fibrous proliferation, endolaser is used to treat the edges of the retinal defects. Long-acting gas or silicone oil¹³ is used for tamponade.

2. Diffuse Contraction (Figure 3)

In the event of large retinal defects with diffuse contraction, two or more rows of treatment by either diathermy or endolaser may be used to completely encircle the defect with extension to the surrounding normal retina. It is often necessary to extend the coagulation to the ora serrata when proliferation involves the vitreous base.

Following adequate diathermy, the subretinal space is entered in any area of elevation without damaging the underlying choriocapillaris. A two-function (illumination/coagulation) or three-function (illumination/coagulation/suction) instrument is used for prompt hemostasis.

Following complete removal of the proliferative membrane and relief of the retinal shortening, endolaser is used to treat the edges of the retinal defect. Due to minimum collateral circulation, the remaining

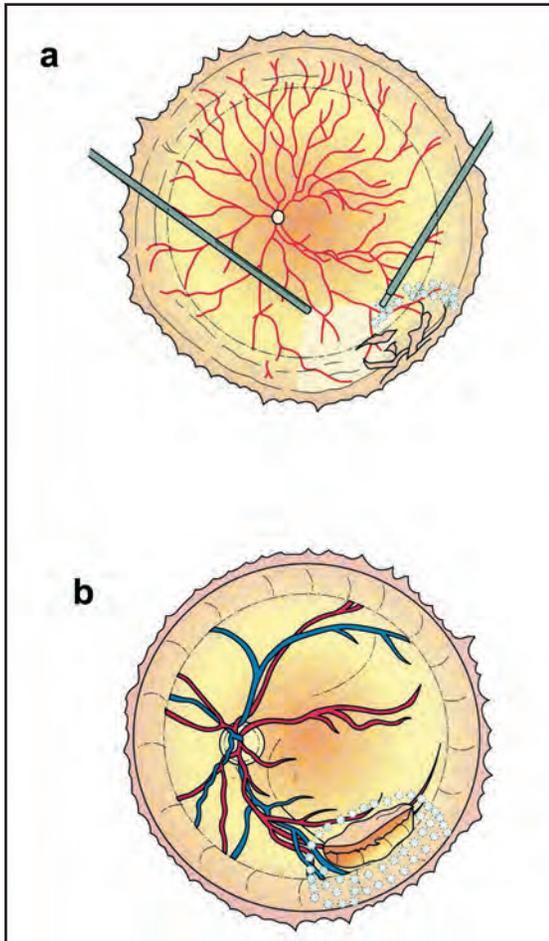


Figure 3: Diffuse Contraction. (a) Diathermy completely encircle the area of proliferation with extension to the surrounding normal retina or to the ora serrata. (b) Large retinectomy surrounded with laser for 360° or to the ora serrata. Contracted retina removed with excision. The edges of retinal defect treated with diathermy, carrying out to the pars plana if retinectomy approaches the vitreous base.

anterior retina is usually treated using laser photocoagulation, cryoablation, or extension of the retinectomy to the ora serrata. When the retinectomy extends to the ora serrata, endolaser or transcleral cryotherapy should be applied across the ora serrata onto the pars plana to avoid accumulation of subretinal

fluid with contraction of the vitreous base. Long acting gas or silicone oil is used for tamponade.

3. Circumferential Contraction (Figure 4)

Significant contraction of membranes at the vitreous base may lead to extensive circumferential contraction. Because the direction of the contraction is anterior-posterior, the posterior hyaloid pulls the retina centrally into a funnel shape. The circumferential contraction is difficult to relieve even with posterior hyaloid excision and membrane dissection, leaving the retina in a contracted state.

A broad encircling scleral buckle is used first, to minimize the contraction. Vigorous and compulsive epiretinal membrane dissection is performed to relieve the residual traction. This may best be achieved with the help of intraoperative intravitreal injections of triamcinolone, indocyanine green, or trypan blue.¹⁴⁻¹⁷ If the contraction is still persistent, then the vitreous is trimmed to the retinal surface, starting at the posterior hyaloid and advancing to the vitreous base. The hyaloid is often adherent to the membrane posterior to the vitreous base. The vitreous base should be shaved down to the retina, facilitated by scleral depression and/or with the use of a wide-angle viewing system.

A retinectomy is indicated when the retinal contraction is not adequately relieved by the above measures. PFCL is injected over the disc and filled toward the level of the residual contraction. The tamponade force of PFCL identifies areas of persistent retinal traction that must be released and stabilizes the

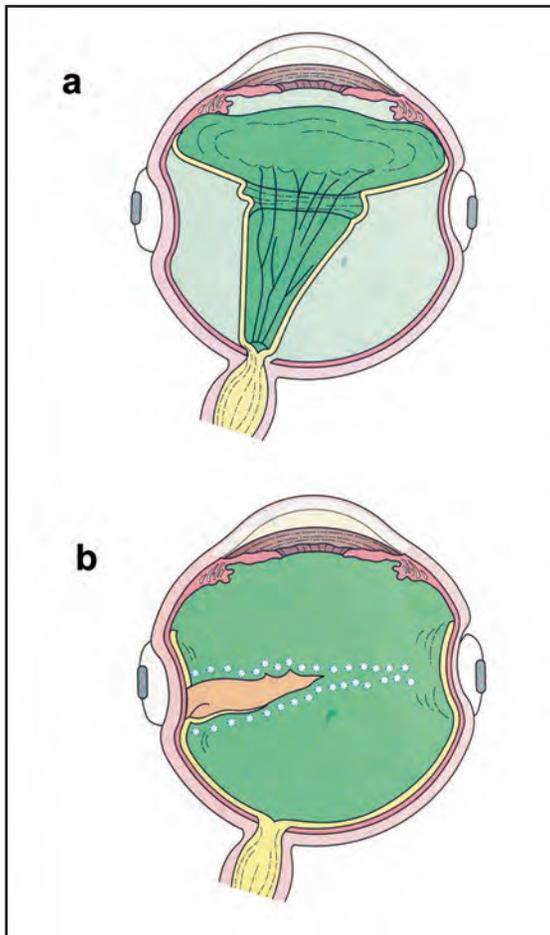


Figure 4: Circumferential Contraction. (a) Circumferential contraction of posterior vitreous base with radial folds. Retina is pulled into funnel configuration. (b) After vitrectomy, membrane peel and scleral buckle, circumferential retinotomy is performed under perfluorocarbon liquid (PFCL) and retina flattens.

retina during retinectomy or further membrane peeling. The height of the scleral buckle can be adjusted at this time to diminish any residual traction. A retinectomy is performed circumferentially and posteriorly into the normal retina. It is important to excise well into the normal retina to ensure proper attachment of the retina once the air or gas

is absorbed. Anteriorly, the retina is excised to the anterior-most level of traction.

4. Anterior Retinal Displacement (Figure 5)

After vitreous manipulation such as pars plana vitrectomy, trauma or pneumatic retinopexy, fibrous proliferation and contractions may occur at the vitreous base and lead to anterior retinal displacement. Pulling of the peripheral retina anteriorly toward the pars plana can lead to retinal detachment. Hypotony often results from fibrous proliferation and contraction over the ciliary body causing a ciliary body detachment.

Pars plana lensectomy is usually required to ensure adequate dissection of the anterior membrane. It is important to remove all lens material including the entire capsule to limit future contraction of the capsular bag.¹⁸ To eliminate the traction that displaced the retina anteriorly, an encircling scleral buckle is used to support the vitreous base. After peripheral vitreous and vitreous base shaving, a limited dissection of the anterior membrane is performed using external indentation and a bimanual internal technique with an illuminated pick or forceps and scissors.

If part of the anterior traction still persists despite the dissection and the scleral buckle, a peripheral retinectomy may be performed in order to relax the retinal traction and facilitate apposition to the underlying RPE. The retinectomy should extend into the normal peripheral retina to avoid any residual proliferative tissue.

Endoillumination may not be adequate in the extremely anteriorly displaced membranes.

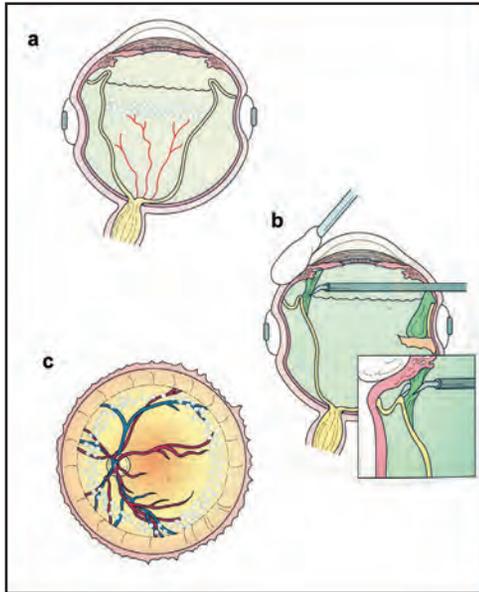


Figure 5: Anterior Retinal Displacement. (a) Diathermy is applied to the area of retinectomy. (b) Anterior retinal displacement is released by removing membrane with scissors. (c) The 360° relaxing retinectomy is completed and photocoagulation applied.

The coaxial light of the operating microscope or external illumination may be the better solution. The use of a panoramic viewing system can greatly improve visualization and facilitate dissection of the peripheral retina.¹⁴

5. Giant Retinal Tear (GRT) (Figure 6)

A giant retinal tear is often accompanied by the inward curling of the anterior retinal edge. The intrinsic elasticity of the retina initiates the curling process, with migration of the RPE cells over the edge to the internal limiting membrane facilitating proliferation and contraction which results in PVR. The direction of traction can be anteroposterior or circumferential. If the retinal traction

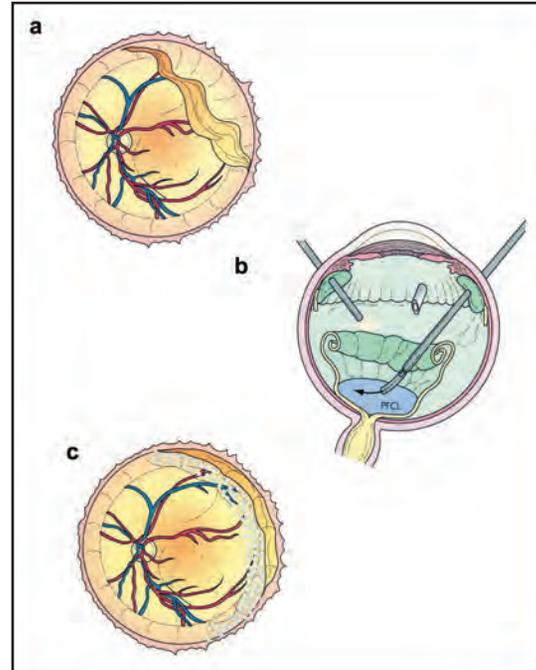
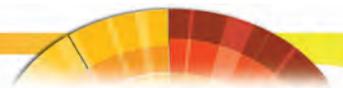


Figure 6: Giant Retinal Tear. (a) Giant retinal tear with fixed rolled edge. (b) Perfluorocarbon liquid (PFCL) is injected over the posterior pole, to the level of the anterior edge of the giant retinal tear, to unfold the flap of the giant retinal tear. (c) Photocoagulation applied to the edges of the giant retinal tear following retinectomy of contracted elements not responsive to careful membrane dissection.

cannot be relieved by scleral buckling and membrane dissection, a retinectomy is needed to facilitate apposition of the retina to the underlying RPE.

Perfluorocarbon liquid is injected over the posterior pole, displacing subretinal fluid anteriorly to uncurl the flap of the retinal tear. Diathermy is then applied to the edges of the giant tear with extension to the normal surrounding retina. The entire proliferated retinal edge is excised to relieve traction. Care is taken not to leave any jagged area behind



to minimize future contraction. With PFCL stabilizing the retina, endophotocoagulation is applied to the entire area of GRT. During the initial phase of the fluid-air exchange, the anterior edge of the GRT is dried by suction with a soft-tipped needle beneath the anterior edge of the retina. Care is taken to ensure proper attachment of the retina in the area of the GRT. The fluid-air exchange is then completed to remove residual PFCL.

6. Subretinal Membranes

The approach to subretinal membranes is based on the location and extent of the membranes. The retinotomy should be made as peripheral as possible. An isolated band that exerts traction or causes tenting of the retina is best reached with a retinotomy adjacent to the membrane, preferably towards the middle of the band. Diathermy is applied to the retina at the selected location, and the diathermy tip can be used to enlarge the full thickness retinotomy. The retinotomy can be further extended if needed with scissors. The membrane is carefully grabbed with intraocular forceps and gently tugged to see if it will come loose. If the membrane can be gently pulled free, the membrane is pulled, regripped, and then the remainder of the band snaked through the retinotomy and removed. The retinotomy should then be walled off with endolaser.

Care should be taken to avoid choroidal hemorrhage with aggressive pulling on the membrane if it is attached to the RPE/choroid. If the membrane will not easily come out, the membrane should be cut with scissors. This technique relaxes the membrane and reduces traction. If sections of the band are more accessible after sectioning, it should

be removed. Choosing to access the band towards its midline has two advantages: (1) long subretinal bands are removed efficiently; (2) if the band is cut with scissors, there is now equal access to two ends of the band. If left behind, traction is likely to be equally relieved.

In the case of a subretinal sheet or napkin ring, a more extensive circumferential retinectomy is required. Endodiathermy is used to mark the location and cauterize blood vessels. Vitrector or scissors can be used to cut along the marked edges of the diathermy. The retina should be folded back on itself to expose the membranes on the undersurface of the retina and the RPE. In conjunction with perfluorocarbon liquids to stabilize the retina, careful dissection is used with bimanual techniques.

PROLIFERATIVE VASCULAR RETINOPATHY / PROLIFERATIVE DIABETIC RETINOPATHY

Although rare, tractional retinal detachment associated with diabetic retinopathy may require retinotomy or retinectomy to relieve traction and facilitate reattachment. In the presence of fibrous proliferation, it is important to relieve all traction when retinal breaks are present. When the tractional retinal detachment extends to the macula area with reduced central visual acuity, an attempt is made to relieve retinal traction and restore macular anatomic integrity.

Due to long-standing ischemia associated with diabetic retinopathy, areas of the retina can become thin and atrophic. Care



should be taken to minimize retinal tearing during surgical manipulation. Diabetic membranes can be segmented or delaminated in most cases to relieve traction. However, when the fibrous contraction from the membrane is associated with a posterior break, a retinectomy surrounding the area of traction may have to be performed to relieve residual traction and promote reattachment.

1. Long-standing Fibrovascular Proliferation

The same principles discussed for PVR apply here. Membrane dissection and scleral buckling are performed first to relieve traction. If traction still persists, a retinectomy is then performed. Diathermy is applied to the membrane and the surrounding retina. Care is taken to minimize the area of retina that needs to be excised. The retinectomy is performed either with a vitrectomy instrument or with scissors, which allows better control and precision. After ensuring the retinal traction is relieved, the edges of the retinal defect are treated with endophotocoagulation and a long-acting gas or silicone oil is used for tamponade.

2. Anterior Hyaloidal Fibrovascular Proliferation (AHFVP)

Similar in clinical appearance to anterior retinal displacement, anterior hyaloidal fibrovascular proliferation (AHFVP) is caused by neovascular proliferation and contraction of the peripheral retina and extends to the anterior hyaloid and along the posterior surface of the lens.^{19,20} With time, the contraction of the fibrovascular tissue pulls the peripheral retina forward leading to retinal detachment.

AHFVP is usually seen in patients with severe proliferative diabetic retinopathy after vitrectomy. It differs from anterior retinal displacement by its prominent vascularity and propensity to bleed.

After a pars plana vitrectomy and lensectomy, a bimanual technique is used to dissect the membrane. Scleral depression of the peripheral fibrous tissue will facilitate visualization and dissection. Because of the high degree of vascularity, diathermy is applied to the vessels to achieve hemostasis before dissection. A two-function (illumination/coagulation) or three-function (illumination/coagulation/suction) instrument will provide readily available diathermy in the event of bleeding. Thrombin may be infused if significant bleeding occurs.²¹

A retinectomy may be indicated if the retina fails to relax despite of careful membrane dissection. Depending on the extent of the contraction, the retinectomy may extend to encircle the peripheral retina. Endophotocoagulation is then applied to the edges of the retinectomy to ensure adequate attachment. Silicone oil is usually used to tamponade the retina and reduce the risk of anterior segment ischemia.

RETINAL INCARCERATION ***(Figures 7 and 8)***

Retinal foreshortening and contraction can occur after open globe injury or inadvertent surgical incarceration. In addition to true retinal shortening due to tissue fixing to the wound site, fibrous proliferation during healing phase may exacerbate contraction. The severity of retinal shortening is dependent

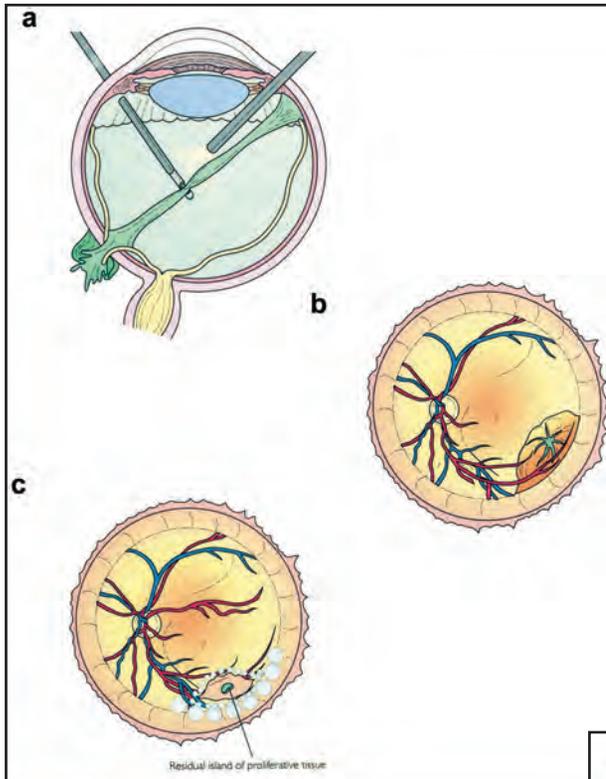


Figure 7: Retinal incarceration. (a) Lysis of incarcerated retina using patchy retinotomy. (b) The proliferation through the exit site is reduced to a stump. (c) Application of diathermy around the wound site after necrotic retina has been removed.

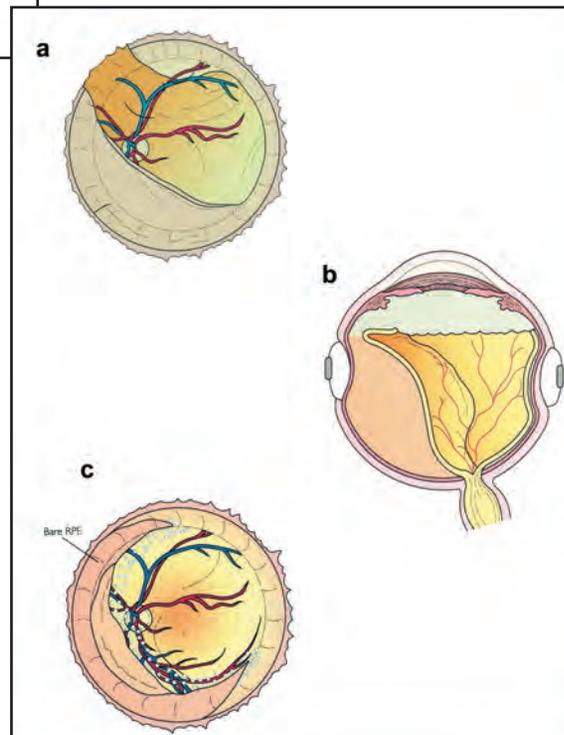


Figure 8: Distal Retinal Incarceration. (a) & (b) Retinal incarceration in the wound on the opposite site of globe. (c) After large retinectomy into the adjacent healthy retina, photocoagulation is applied to the edge of the retinal defect. Bare retinal pigment epithelium is seen nasally.



on the size, location and chronicity of the wound. A retinectomy is usually indicated to relieve traction and facilitate reattachment of the retina.

After a standard three port pars plana vitrectomy, the wound is explored for its size, location and signs of chronicity such as the presence of retinal folds. Every attempt should be made to avoid inadvertent entrance into the subretinal space with the vitrectomy instrument, especially during traumatic repair when reduced visualization is a common occurrence.

If the wound is recent and no fixing of the retinal tissue to the wound is detected, the focus of incarcerated retina can be carefully teased out of the wound. Perfluorocarbon liquids (PFCL) may be used to facilitate the process.

In most traumatic cases, however, incarcerated retina must be excised because the retina cannot be dislodged from the wound site. After diathermy is applied carefully to encircle the area of incarceration, a scissors blade or a membrane pick is used to enter the subretinal space tangentially through the necrotic retina. The retina is carefully lifted away from the RPE before cutting. Repeated diathermy may be needed while cutting the retina in an annular fashion until the necrotic retina has been excised 360° around the wound site. PFCL, injecting over the posterior pole, may facilitate the attachment of the retina around the wound site. The edges of the retinal defects should be treated with endolaser and the eye filled with a long-acting gas or silicone oil.

Complications

Hemorrhage is one of the major complications of retinotomy. Non-resolving intraoperative and postoperative hemorrhage can lead to fibrin formation and fibrous proliferation impairing final surgical outcome. To achieve complete hemostasis, meticulous application of diathermy is of significant importance. A continuous row of diathermy to the surrounding vessels is usually obtained before cutting, to minimize future oozing. However, care is taken to avoid excessive diathermy, which could lead to tissue necrosis.

In the event of hemorrhage during a retinectomy, infusion pressure should be raised, increasing intraocular pressure. In addition, use of a combination diathermy and a fiberoptic light source or a three-function tissue manipulator provides ready access to diathermy. Thrombin can be infused in the vitreous cavity in case of significant persisting hemorrhage.²¹

The incidence of hypotony (intraocular pressure less than 5 mmHg) is reported to be as high as 43% by Morse et al.²² It is more commonly seen after large retinotomies. Possible mechanisms include anterior fibrous proliferation leading to detachment of the ciliary body and less likely, increased absorption of intraocular fluid from the largely exposed RPE.

Retained subretinal or preretinal perfluorocarbon liquid may lead to retinal toxicity and contribute to poorer visual acuity if subfoveal.²³ Retained subretinal perfluorocarbon liquid bubbles most frequently occur in cases of large peripheral retinotomies/



retinectomies. The incidence has been associated with retinotomies greater than 120 degrees and reported to be as high as 40% in eyes with a 360-degree retinotomy.²⁴ Posterior small retinotomies usually do not increase the risk of subretinal PFCL.

Recurrent retinal detachment due to failure to relieve traction may occur if the retinectomy is too small and membrane dissection is incomplete, leaving fibrous proliferative tissue behind. To avoid such occurrence, retinectomy should be extended well into the normal retina in all directions to relieve traction. In addition, meticulous bimanual membrane dissection is imperative in complete removal of residual fibrous proliferative tissue.

Surgical Results

In 1986, Machemer et al reported the results of relaxing retinotomies in 56 eyes that had not been successfully repaired by conventional procedures.² At the end of a 6-month follow-up period, the rate of retina attachment was 40%, and visual acuity was 5/200 or better in 6.7% of the eyes.

In 1990, Morse et al reported 100 eyes undergoing relaxing retinotomies in a retrospective series.¹⁸ At 6 months follow-up, 58 eyes were completely attached and 8 eyes had partial reattachment with the macula on. At the final follow-up, 29 eyes achieved visual acuity of 5/200, 17 eyes had 20/200 or better vision, and 5 eyes achieved better than 20/100 vision. The length of the retinotomy did not appear to affect the surgical outcome in the study. A radial relaxing retinotomy or a relaxing retinotomy involving the entire

temporal quadrant was, however, associated with poorer visual outcomes.

Similar results were reported by a case series by Han et al.²⁵ Relaxing retinotomies were performed on 54 consecutive eyes (42 eyes for PVR and 12 for trauma) with a minimum follow-up of 6 months. 35 eyes (64%) achieved anatomic success (retina remained attached posterior to the scleral buckle with an intraocular pressure of 3mmHg or more). Visual acuity of 5/200 or better was achieved in 14 eyes (26%). Superior location of the relaxing retinotomy and preoperative visual acuity of hand motion or better are associated with better visual outcomes.

The Silicone Study, a multicenter, randomized, prospective clinical trial, evaluated the use of silicone oil and long-acting gas in eyes with severe PVR and helped to define the expected outcome for vitrectomy in these eyes.²⁶ One hundred seventeen eyes with severe proliferative vitreoretinopathy were treated with vitrectomy, underwent a relaxing retinotomy, and received either perfluoropropane gas (C3F8) or silicone oil. 46 eyes (20%) had no previous vitrectomy (group 1); 71 eyes (42%) had undergone previous vitrectomy (group 2). At the end of 6 months, 58% had anatomical attachment, 38% achieved visual acuity of 5/200 or better, 31% were hypotonic and 35% had corneal opacities.

A more recent report demonstrated high anatomical success and low rates of hypotony using combined circumferential retinectomies with radial relaxing retinotomy. Twenty-seven of thirty eyes (90%) with advanced PVR and circumferential foreshortening achieved retinal flattening with 6 months follow up without support from a scleral buckle. Median visual acuity was counting fingers.²⁷



Quiram et al²⁸ report the results of inferior retinectomy for PVR and factors that may be associated with better anatomical success. Ninety-three percent of patients were anatomically attached by most recent follow up (mean 25 months) including 40% requiring additional retinectomy surgeries. Five of their patients underwent 3 or 4 retinectomy surgeries. In 70% of their patients, visual acuity remained stable or improved. They report that radical 360-degree anterior vitreous base dissection combined with lens removal had better surgical anatomical outcomes. Twenty-six of 35 (74%) patients who underwent 360-degree anterior vitreous base dissection with lens removal remained attached compared to 8 of 21 (38%) ($p = 0.011$) patients that did not.

Conclusion

Relaxing retinotomies and retinectomies are procedures to consider when other less aggressive measures fail in attempts to treat complex retinal detachments. Previously associated with dismal anatomical and visual results, the advancement of surgical methods and adjuncts have shown significant improvement in anatomical and functional success of retinal detachments associated with severe PVR and contraction.²⁹

Scleral buckle and aggressive membrane dissection should be performed first to relieve retinal traction and minimize fibrous proliferative tissue. In eyes with severe PVR, proliferative vascular retinopathy or retinal incarceration, retinotomies and retinectomies are often needed to further relieve the traction and facilitate reattachment. Aggressive

anterior vitreous base dissection combined with lens removal may increase re-attachment rates.

Relaxing retinotomies are most commonly performed circumferentially rather than radially. With the assistance of intraoperative PFCL, endocoagulation and long-acting gas or silicone oil tamponade, retinectomies have achieved better surgical success rate over the last decade. Using better techniques, instruments and adjuvants, the eyes that were once considered irreparable now have an opportunity for useful ambulatory vision.

Acknowledgments

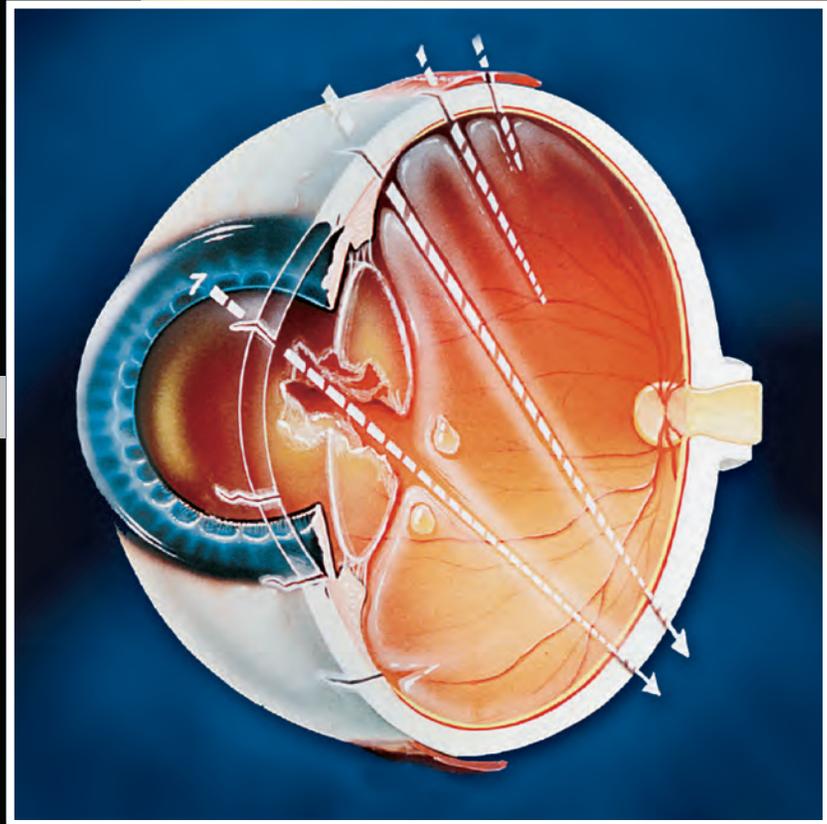
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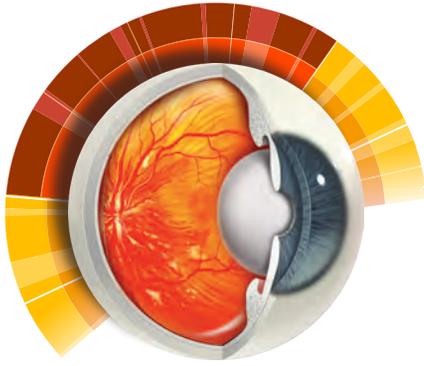


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Section 8

Management of Complex Cases



29

Dislocated IOLs and Crystalline Lens

SAMUEL BOYD, MD

While phaco tools, lenses and surgical techniques have advanced sufficiently to make cataract surgery an outpatient procedure, there has also been a creep up in some post-surgical complications. We have learned over time that certain conditions, like pseudoexfoliation, are associated with a progressive contracture of the anterior lens capsule following surgery.

Dislocated Crystalline Lenses

The loss of the cataractous lens or nuclear fragments into the vitreous is one of the most serious complication during surgery. As surgeons convert from extracapsular cataract surgery to phacoemulsification, an increased number of cases of dislocated cataract occur during the fragmentation phase of the surgical procedure. The displaced fragment may involve the entire nucleus or any fragment

of it. As anterior segment surgeons become more skilled with phacoemulsification, the incidence of dislocated fragments decreases. The estimated incidence of this complication is about 0.3%.

Main Causes

Zonular Disinsertion

Zonular disinsertion is always a risk because separation of the nucleus from the cortex is necessary. Zonular rupture may occur during rotational or see-saw mechanical manipulations of the nucleus by the phacoemulsification tip, or by a second instrument.

During central sculpting of the nucleus too much posterior, as well as inferior pressure,



can be applied with the phacoemulsification tip, resulting in a disinsertion of zonular ligaments around the superior part of the lens. In order to avoid undue stress on the zonular ligament fibers, the phacoemulsification tip should not be advanced any faster than the rate at which it can nibble its way through the nucleus. The movements must be slower and more gentle with dense lens material than with the more typical moderate nuclear sclerosis.

Posterior Capsule Rupture

The risk of posterior capsule rupture, during deep central sculpting, is not as great with firm lenses as it is with those with moderate lens density. With a thick, soft epinucleus, the sculpting may unexpectedly break through this softer material and extend through to the posterior capsule quickly. Positive posterior (vitreous) pressure and high myopia increase the risk of posterior capsule rupture. Because of this added risk, and because deep sculpting through this soft material is unnecessary with modern techniques, one should only sculpt as deeply as is required to be able to fracture the nucleus easily.

Failure to recognize a discontinuity or actual tear in the anterior capsule, can lead to a serious complication during surgery - an anterior capsule tear, which extends around the equator to the posterior capsule. This type of tear has the greatest potential for causing loss of nuclear fragments into the vitreous (Figures 1 and 2). In the presence of an anterior capsular tear, the entire nucleus should be removed by gentle sculpting while

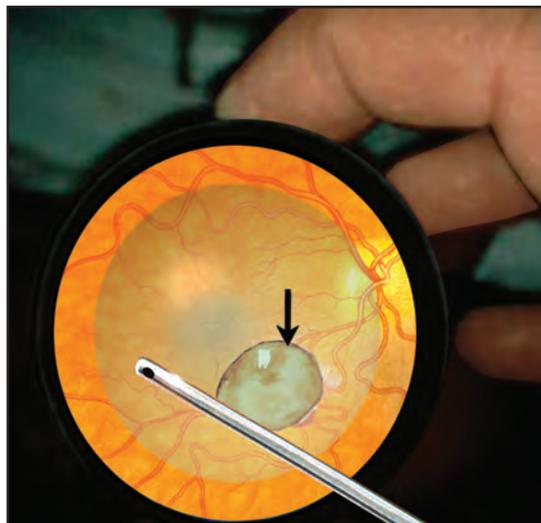


Figure 1: Use of Perfluorocarbon Liquid for Dislocated Lens Removal - Initial Stages. The surgical technique involves a three-port pars plana vitrectomy with removal of as much as possible of the base of the vitreous gel prior to removal of the lens. After the vitreous has been removed, perfluorocarbon liquid is injected over the optic nerve head to float the dislocated lens off the retina and into the anterior vitreous cavity. The dislocated lens is then fragmented in the anterior vitreous cavity while floating on the perfluorocarbon liquid. If small fragments of nucleus drop onto the perfluorocarbon liquid, as shown in this figure, they are then removed either by aspiration or fragmentation. Perfluorocarbon liquid (P). Lens Fragments (L). Phacofragmentation tip (A). Tissue manipulator (cannula with endoilluminator) (E). Infusion cannula (I). (Art from Jaypee - Highlights Medical Publishers).

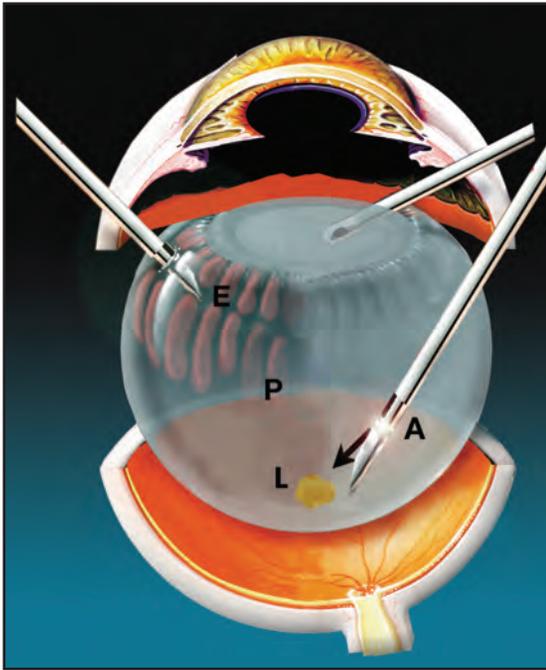


Figure 2: Use of Perfluorocarbon Liquid for Dislocated Lens Removal - Final Stages. The last lens piece (L) is shown being aspirated from the eye with the phacofragmentation tip (A) as it floats on the perfluorocarbon liquid (P). Tissue manipulator (cannula with endoilluminator (E)). If a retinal detachment is present, the perfluorocarbon liquid will displace the subretinal fluid through the pre-existing anterior retinal break and into the vitreous cavity, thereby reattaching the retina. (Art from Jaypee - Highlights Medical Publishers).

stabilizing the nucleus with a second instrument to avoid pressure against the equator of the capsule.

By utilizing the newer methods in phacoemulsification for breaking up the nucleus, the risk of posterior capsule rupture should be significantly diminished. Techniques

have evolved since the original phaco chop described by Nagahara. Some surgeons do a pre-chop, by which the nucleus is actually chopped before the phacoemulsification is begun.

These advances reduce the amount of phaco-energy that must be delivered to the eye and make the surgery safer. Because there are fewer manipulations, cracks and other complicated maneuvers inside the eye, less stress is placed on the capsule and zonules.

Indications for Removal of Dislocated Lenses

Not all dislocated cataractous lenses need to be removed. If they have been present in the vitreous cavity for a long period of time and are causing no complication, it is not necessary to remove them. However, in the majority of cases, the material dislocated into the vitreous cavity has to be removed. The general indications for removing dislocated lenses includes impaired visual acuity, resulting either from obstruction of the visual axis by the dislocated lens or the development of complications. The latter may refer either to those already occurring or to the early signs of potential for development of complications such as phacolytic uveitis, glaucoma, corneal edema, retinal tears and detachment, vitreous hemorrhage or cystoid macular edema. The degree of intraocular inflammation usually reflects the size of the retained lens fragment, the time interval since cataract surgery, and individual inflammatory reactivity. If any of these complications has occurred or is likely to develop, the dislocated lens or fragments must be removed from the eye.



Management of Dislocated Lenses

Once posterior capsule rupture occurs, the surgeon must proceed with extreme caution, using a limbal approach to retrieve lens fragments. In this situation, placing a dense viscoelastic in the anterior chamber, and using an adequate micro forceps to handle nucleus fragments, allow removal of the fragments before they migrate to a position posterior to the capsule. Once the fragment drops toward the vitreous cavity, the maneuvers to retrieve this fragment from this location increase the risk for retinal tears and detachment, and should be avoided. The surgeon can continue the surgery by placing a posterior chamber intraocular lens if there is residual peripheral capsule that could support the lens. If the remaining capsule is insufficient, the surgeon should consider a scleral sutured-IOL, placing an anterior chamber intraocular lens in the eye, or not to place an IOL, closing the eye, and referring the patient to a retinal surgeon, within a week, for appropriate management. The anterior segment surgeon should avoid panic. We emphasize that he/she should not try to remove the dislocated crystalline lens from the vitreous cavity, because of the possible development of a giant retinal tear, retinal detachment, or hemorrhage, which could lead to permanent visual damage. The vitreoretinal surgeon can handle the patient's eye from a posterior segment point of view, and visual results often are excellent.

Today, most highly experienced vitreoretinal surgeons use perfluorocarbon liquids in management of patients with dislocated crystalline lenses (Figures 1 and 2). The physical properties of perfluorocarbons make

them far superior and safer than previous techniques for managing dislocated lenses. Other methods have been abandoned because of their limitations, complexity and complications.

Liquid perfluorocarbons, which are heavier than water, lifts the crystalline lens from the retina into the anterior vitreous cavity (Figures 1 and 2) The high specific gravity of these liquids exerts a flattening force that reattaches the retina while the lens is being lifted in cases in which there is a concomitant retinal detachment. The viscosity of perfluorocarbons provides a cushion that supports the lens and prevents retinal damage from falling lens fragments, thus, the potential for retinal damage is significantly reduced.

Surgical Technique

The surgical technique involves a three-port pars plana vitrectomy with removal of as much as possible of the basal vitreous gel prior to the removal of the lens. Adequate initial vitrectomy avoids unintended vitreous traction during phacofragmentation. After the vitreous has been removed, perfluoro-n-octane is injected over the optic nerve head to float the dislocated lens off the retina and into the anterior vitreous cavity (Figure 1). This is an effective method that significantly reduces the inflammatory response and hastens visual recovery.

If a retinal detachment is present, the perfluorocarbon liquid will displace the subretinal fluid through the preexisting anterior



Figure 3: Perfluorocarbon Liquid used to Remove Dislocated Nucleus Fragments. If a retinal detachment is present, the perfluorocarbon liquid will displace the subretinal fluid (arrow) through the preexisting anterior retinal break (R) and into the vitreous cavity, thereby reattaching the retina. The dislocated lens (N) is then fragmented in the anterior vitreous cavity while floating on the perfluorocarbon liquid (PFC). (Art from Jaypee -Highlights Medical Publishers).

retinal break and into the vitreous cavity, thereby reattaching the retina. (Figure 3). The dislocated lens is then fragmented in the anterior vitreous cavity while floating on the perfluorocarbon liquid. The lens, or lens fragments have to be kept in position with the help of a second instrument. An illuminated hook-probe is usually sufficient for this maneuver. The intermittent pulsed ultrasound-mode, with reduced ultrasound power (5%-10%), helps to keep the fragment

occluding the tip, and minimizes the chance of fragments dropping back onto the retina, even though they rarely strike the retina with sufficient force to damage it. If small fragments of nucleus drop onto the perfluorocarbon liquid, they are then removed either by aspiration or fragmentation (Figure 4). Fragments should be cautiously aspirated from the retinal surface and moved to the mid vitreous before ultrasonic fragmentation, to avoid suction or ultrasonic damage to the retina. For very small fragments, it is better to aspirate with the vitreous cutter-probe.

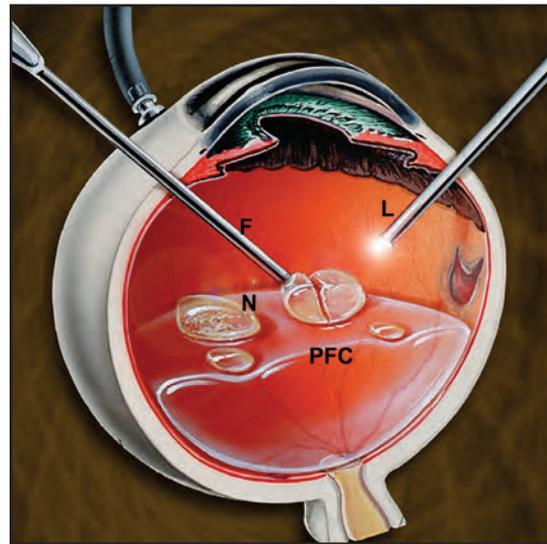


Figure 4: Extraction of Nuclear Fragments. The availability of modern phacoemulsification units generally precludes the need for external incisions to extract pieces or fragments of nucleus (N). Either way, they still are options when fragmentation devices (F) are unavailable, or in cases with extremely hard nuclear fragments and in cases of dislocated intraocular lenses. Perfluorocarbon liquid (PFC). Endoillumination (L). (Art from Jaypee - Highlights Medical Publishers).



If the basal vitreous gel is not debulked prior to the lens fragmentation, small fragments of lens may become embedded in it. Retinal damage can occur when these fragments are being removed. It is therefore important to remove as much as possible of the base of vitreous gel at the beginning of the operation before the dislocated crystalline lens is removed. If the lens is very firm and difficult to fragment, mechanical crushing between two instruments may be used. If the lens is too hard and the surgeon cannot fragment it in the anterior vitreous cavity, then it must be floated with the perfluorocarbon liquid until it lies just beneath the pupillary margin. If the entire lens is being removed the retinal surgeon may employ a phacofragmentation or phacoemulsification technique, where mechanical ultrasound is used to first break up the lens.

After the vitrectomy and removal of the lens-fragments has been completed, if an IOL was not inserted during the previous cataract surgery, the placement of an IOL has to be considered. If there is sufficient capsular support, the IOL is placed in the posterior chamber; if not, suture-fixation techniques may be used. An open-loop anterior-chamber lens insertion is a viable option in the absence of an adequate capsular-support.

Outcome After Surgery

The visual results of managing cases of posteriorly dislocated or retained lens fragments are generally good. A postopera-

tive visual acuity of 20/40 or better has been reported in 42% to 88% of the patients.

Postoperative complications include cornea edema, glaucoma, persistent intraocular inflammation, and retinal detachment. Retinal detachment coexists with retained lens material in 8.0% of reported series, and retinal detachment has been reported after vitrectomy for removal of retained lens fragments, in 8.3%. It is of critical importance to evaluate the retina throughout the perioperative course in these patients.

Combine Clear or Opaque Lens Extraction, IOL and Pars Plana Vitrectomy

When is Lensectomy Indicated

An important issue that warrants consideration is determining when a lensectomy is indicated, whether the lens is clear or opaque. During vitreoretinal surgery to repair a diabetic traction or combined traction and rhegmatogenous retinal detachment, the indications for lensectomy are limited to the following conditions:

- 1) A cataract that will prevent visualizing the posterior retina and reattaching the retina.
- 2) Eyes with fibrovascular membranes extending anteriorly on the retina, in which case the clear lens has to be removed in order to release the traction on the anterior retina.

In these cases it is better to sacrifice a clear lens than to leave persistent traction on the retina, which will eventually lead to a posterior retinal detachment and surgical failure. If a lensectomy is performed, it is extremely important to perform extensive endophotocoagulation to decrease the risk of developing neovascular glaucoma.

Implantation of Intraocular Lens - Different Options

During combined lens removal and pars plana vitrectomy, implantation of an intraocular lens can be considered. The decision is made intraoperatively after the surgeon has had the opportunity of determining whether there is good visual potential. If the retina appears relatively healthy, there is not a significant amount of fibrovascular tissue, and the surgeon believes that it is likely that the patient will have a good visual rehabilitation, then a posterior chamber intraocular lens should be considered for implantation.

Different surgical options may be used to successfully insert posterior chamber lenses during combined lens removal and pars-plana vitrectomy.

Option 1: A phacoemulsification technique is (Figure 5) followed by standard pars-plana vitrectomy and laser endophotocoagulation. The intraocular lens implantation is done after the vitrectomy and

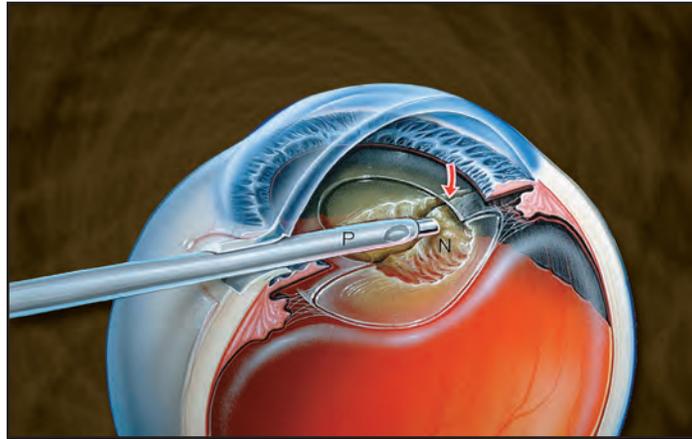


Figure 5: Phacoemulsification in Combined Lens Removal and Pars Plana Vitrectomy - Removing the Nucleus Within the Capsular Bag. This 3/4 cross section view shows the phacoemulsification probe (P) removing the nucleus (N) within the capsular bag. Note the crack (arrow) created in the nucleus. The epinucleus and cortex will then be removed with the phaco probe. In Option 1, this phaco technique is followed by standard pars plana vitrectomy and laser endophotocoagulation. The intraocular lens implantation is done after the vitrectomy and endophotocoagulation is completed. (Art from Jaypee - Highlights Medical Publishers).

endophotocoagulation is completed (optional). The advantages of this technique are that it uses combined standard and commonly performed procedures and permits retention of an intact barrier of zonular fibers and



capsule separating the anterior and posterior segments of the globe, and placement of the posterior chamber intraocular lens within the capsular bag. The posterior capsule is left intact. It also has the advantage of allowing the vitrectomy procedure to be completed, the fundus examined and operative complications identified, evaluated, and corrected before the decision is made to insert an intraocular lens. The disadvantage of this technique in a relative way, include the presence of a limbal

incision that may leak during the vitrectomy procedure.

This disadvantage can be eliminated if a stitch is sutured to close the incision (Figure 6 A-B). If the decision has been made to place a posterior chamber intraocular-lens, the incision can be slightly enlarged if needed, and an intraocular lens placed in the bag.

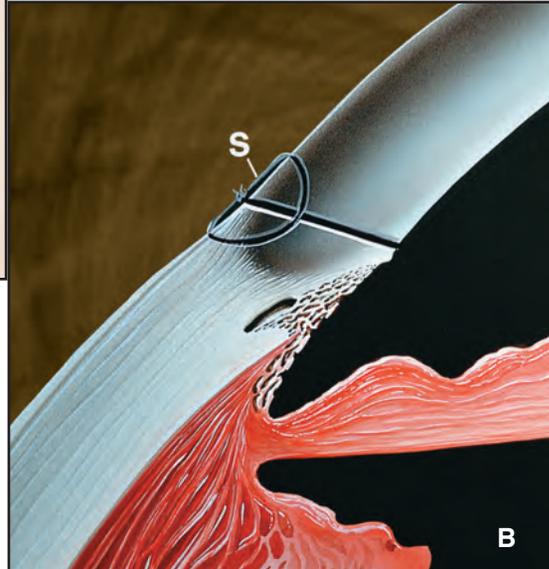
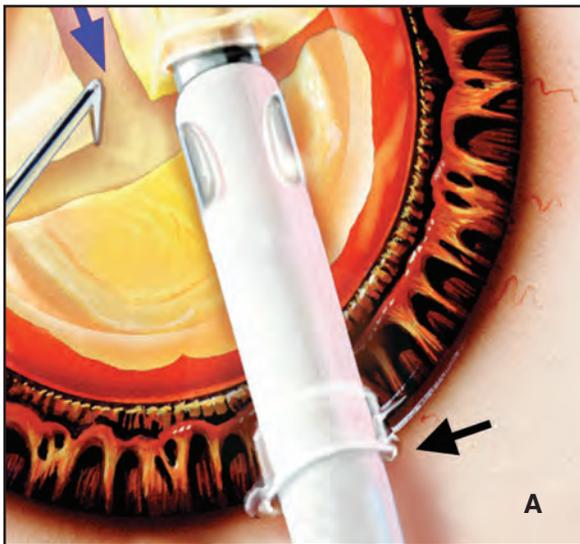


Figure 6 A-B: Limbal Incision for Phacoemulsification - **A)** Surgeon's View. **B)** Cross section view showing single plane architecture of this incision which requires a suture (S) to close. (Art from Jaypee - Highlights Medical Publishers).

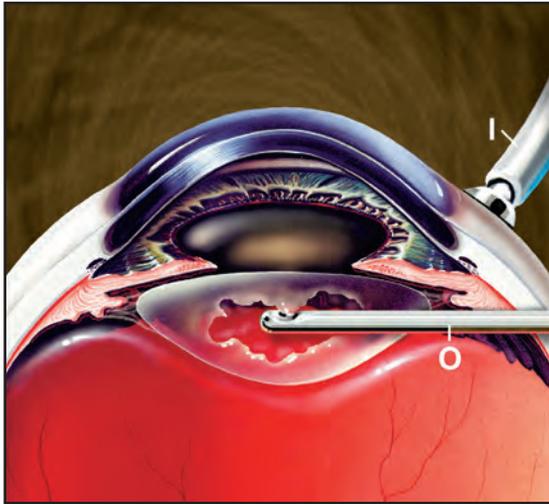


Figure 7: Combined Pars Plana Cataract Extraction and Vitrectomy - Removal of Nucleus and Cortex. In cases of pars plana vitrectomy requiring lens removal, the lens may be removed through the pars plana approach. A phacoemulsifier, aspirating cannula fragmentator or vitreous cutter (O) shown, removes the nucleus and cortex. Infusion is supplied through a separate terminal (I), which will also be used during the vitrectomy stage of the operation. (Art from Jaypee - Highlights Medical Publishers).

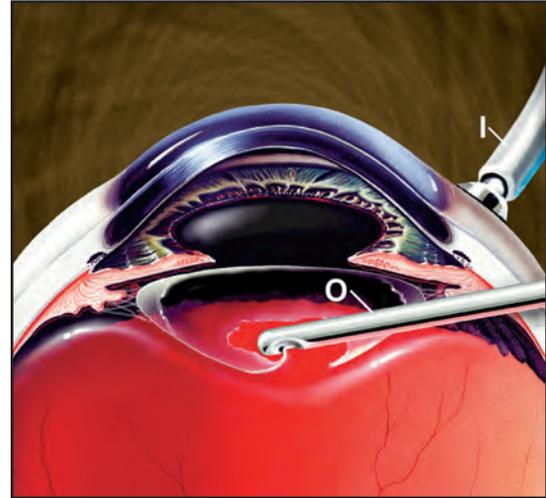


Figure 8: Combined Pars Plana Cataract Extraction and Vitrectomy - Removal of the Posterior Capsule. When planning to insert an intraocular lens, an adequate capsular support is preserved, if possible. Some surgeons prefer to remove the posterior capsule as shown, through the pars plana with the vitreous cutter (O). Following the pars plana vitrectomy, if a decision is then made to implant an intraocular lens, a limbal incision is performed and an intraocular lens is placed over the intact anterior lens capsule. Pars plana infusion terminal (I) is used for both the lensectomy and the vitrectomy. (Art from Jaypee - Highlights Medical Publishers).

Option 2: This technique involves removal of the cataract by phacoemulsification or aspiration through the pars-plana sclerotomies that are used for the subsequent vitrectomy procedure (Figure 7). During this fragmentation or aspiration of the lens, the anterior lens capsule is left intact, but cortical and nuclear aspects of the lens, as well as the posterior capsule, are removed (Figure 8). Then a pars-plana vitrectomy

is performed, and the entire vitreoretinal procedure is completed. If a decision is then made to implant an intraocular lens, a limbal incision is made, and an intraocular lens is placed over the anterior lens-capsule. Then the vitreous cutter is used to make a central opening in the anterior lens-capsule. This technique is welcomed by vitreoretinal surgeons who do not have experience in performing phacoemulsification.



When Not to Implant an IOL

There is general agreement that intraocular lenses should not be placed in eyes with iris or angle neovascularization in eyes with extensive neovascularization of the vitreous cavity, in eyes with extensive retinal detachments, or in eyes with complications occurring during surgery. If there is any doubt, it is better not to implant a posterior chamber intraocular lens and to rehabilitate the patient with a contact lens.

Dislocated Posterior Chamber IOLs

Postoperative decentration of posterior chamber intraocular lenses occurs in 0.2 to 1.8% of cases. If the patient's visual acuity is satisfactory treatment usually is not required. Dislocation into the vitreous cavity is much less common but may induce major complications; its frequency appears to have increased in the past few years because of the following reasons:

- 1) Phacoemulsification has a steep learning curve, and as it becomes more popular, more complications are occurring;
- 2) Surgeons are becoming more reluctant to place anterior chamber intraocular lenses;
- 3) Aggressive placement of posterior chamber IOL in the presence of capsular tears has become more common;

- 4) Silicone - plate IOLs have become more popular.

The posterior chamber implant may dislocate into the vitreous cavity at the time of surgery, or many months after surgery (Figure 9). During cataract extraction dislocation usually results from posterior capsular rupture. Following surgery, complete dislocation usually is observed during the first week after surgery, and may be due to unrecognized posterior capsule rupture, or unstable capsule, although the capsular support may seem to be satisfactory at the time of the initial surgery. Late dislocation is less common and may be due to progressive zonular dehiscence, as in eyes with pseudoexfoliation syndrome, trauma, and asymmetric haptic placement. IOL dislocation may also occur after Nd:YAG laser capsulotomy.

Clinical Findings

After dislocation, a sudden loss of vision, due to the uncorrected aphakia, is noticed by the patient. If the intraocular lens is mobile in the vitreous cavity, the patient may complain of an unusual floater or optical effects. An intraocular lens rarely dislocate completely onto the retinal surface; it usually lies meshed into the anterior vitreous with one haptic still adherent to the capsule or iris. Occasionally the IOL may induce some complications such as retinal detachment or cystoid macular edema secondary to vitreous changes, vitreous hemorrhage, pupillary block, or corneal contact with secondary edema. The presenting

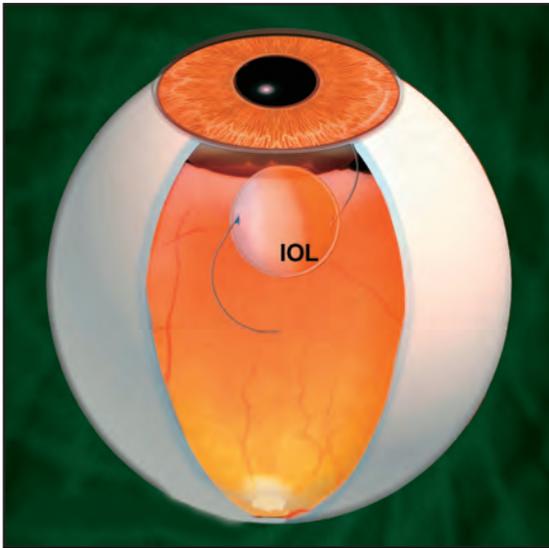


Figure 9: Dislocated Intraocular Lens into Vitreoretinal Cavity. The posterior chamber implant (IOL) may dislocate into the vitreous cavity at the time of surgery, or months later. During cataract extraction dislocation usually results from posterior capsular rupture following surgery. (Art from Jaypee - Highlights Medical Publishers).

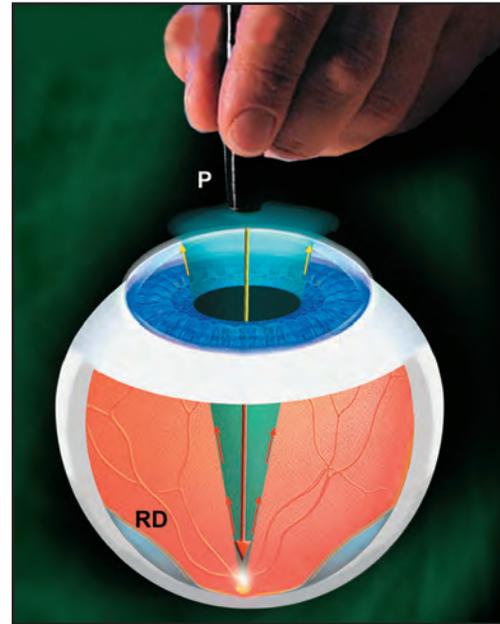


Figure 10: B-Scan Ultrasound used in Dislocated Intraocular Lens. If a vitreous hemorrhage or severe corneal edema is present, a B-scan ultrasound (P) should be used to determine the position of the IOL, and to rule out the possibility of a retinal detachment (RD). (Art from Jaypee - Highlights Medical Publishers).

visual acuity with aphakic correction may be very good, but it is commonly decreased to a moderate degree despite the best spectacle correction. The IOL may be freely mobile in the vitreous cavity, it may be in apparent contact with the retina, or it may have one haptic attached to the posterior capsule, iris, or ciliary body. If a vitreous hemorrhage or severe corneal edema is present, B-scan ultrasound should be used to determine the position of the IOL, and to rule out a retinal detachment (Figure 10).

Management

If the patient's visual acuity is satisfactory with a contact lens or he or she is able to wear aphakic contact lens, the IOL is not mobile, and there are not associated complications, observation is an option (usually this is not the case). If the dislocated intraocular lens interferes with the vision and visual rehabilitation is needed, or if there are associated complications such as vitreous



hemorrhage, retinal detachment, and cystoid macular edema, surgery has to be considered.

There are three surgical options:

- 1) IOL removal,
- 2) IOL exchange,
- 3) IOL repositioning.

(Editor's Note: If the IOL is located in the vitreous cavity, the anterior segment surgeon should avoid maneuvers trying to recover the IOL, because of the high risk of complications. The preferred approach is to close the wound, prescribe the usual topical medications, and refer the patient to a vitreoretinal surgeon. Of all the surgical options, it is generally felt that repositioning of the dislocated IOL, provides the most advantages. One of the problems associated with removal, exchange, or repositioning, of a posteriorly dislocated IOL is the potential for causing complications such as vitreous hemorrhage, contusion of the retina, retinal breaks, and retinal detachment. In the presence of complications such as complex retinal detachment, it is better to remove the IOL, to repair the detachment, and later on, make a decision regarding the best approach to visual rehabilitation.

It is recommended to calculate the power of the IOL preoperatively because an IOL exchange may be necessary if the first IOL is damaged during surgical manipulation.

Surgical Technique

If the anterior capsule and zonular rings are mostly intact and appear sufficient for adequate stability, the IOL may be repositioned into the ciliary sulcus. Repositioning of the IOL into the ciliary sulcus, or over capsular remnant with less than a total of 6 clock hours of inferior capsular support, is not a stable situation. Many of those repositioned IOLs will end up dislocating again. The surgical technique consists of a three port pars plana approach; a vitrectomy is performed; if the vitreous is still attached to the retina, by using high suction with the vitreous cutter, or any other technique, the posterior hyaloid is removed. After the IOL is mobile and free of vitreous adhesion, removal of as much the basal vitreous as possible is recommended. The use of aspiration or perfluoro-n-octane, which is injected between the lens and the retina to float the dislocated IOL, and to protect the retina, has been recommended. These lenses often "skate or glide toward the periphery" on the bubble of perfluoro-n-octane, and its use is not required in most cases. The IOL is grasped with a forceps; silicone lenses are slippery and it may be necessary to use a serrated or diamond-dusted forceps for its manipulation. A wide-angle viewing system is an advantage for this surgical maneuver. The lens is then manipulated into the ciliary sulcus. One haptic may be brought in front of the iris and the other may be positioned in the sulcus, and then, using a bi-manual maneuver, the anterior haptic is brought to



the opposite sulcus (if enough capsular support has been preserved, suturing of the lens may not be necessary).

For removal, or exchange of the IOL, after the IOL is in the anterior chamber, a limbal incision of adequate size, which has been previously prepared, is open and the IOL removed (entirely or cut in half). At this point, for protection of the endothelium, a dense viscoelastic is necessary. If there is another AC or posterior chamber IOL in place, the IOL dislocated in the vitreous cavity may be removed through a pars-plana incision.

If there is not enough capsular support transcleral sutures are necessary. An alternative is to remove and exchange the IOL with an anterior chamber (AC) lens, which may be easier and less traumatic to the corneal endothelium; newer AC IOLs, with flexible open loops, reportedly avoid complications caused by the mechanical side effects of earlier designs. The author prefers scleral suturing techniques with posterior chamber lenses.

Several techniques for IOL suturing have been described. Iris fixation for dislocated PC lenses requires that a suture pass through cornea and iris, around the IOL haptic, and back out through the iris and cornea. Concern regarding iris-mediated chronic inflammation and the technical difficulty encountered during suture placement have led to the development of other techniques.

If the IOL has positioning holes, Hilel Lewis described the following technique: Once the lens has been repositioned onto the residual posterior capsule or, if it is absent, in the ciliary sulcus, the haptics are rotated,

using two reverseinsky hooks introduced through the horizontal sclerotomies, until they are in the vertical meridian and the holes of the optic in the same meridian as the horizontal sclerotomies. This technique may also be used to engage the haptic of the IOL. Single armed 9-0 prolene suture ends are grasped with intraocular forceps and introduced through the sclerotomies. They are passed through the positioning-holes from posterior to anterior. The sutures are tied to the sclerotomies under scleral flaps previously prepared. This technique requires using perfluorocarbon liquids to place the implant in a convenient positioning for suturing.

A safe technique recommended by W. Smiddy and H. Flynn is by using a disposable 27-gauge needle with a hole located in the bevel, which is threaded with 9-0 polypropylene suture and introduced into the eye, 1 mm posterior to the limbus, in the bed of a partial-thickness scleral flap. Slack is created in the suture along the shaft of the needle by withdrawing it slightly. The IOL haptic is guided through this loop by using the intraocular forceps to grasp the optic. The haptic is captured in the loop as the needle is withdrawn (Figure 11). (An alternative is to use a 9-0 or 10-0 prolene suture threaded retrograde up the bore of a five-eighths-inch 25-gauge needle. The end of the suture, that is not threaded, is retrieved through the hub of the needle. This results in a suture loop). A partial-thickness scleral needle passes in the bed of the scleral flap and allows fixation of the scleral suture. A similar procedure is repeated for the other haptic (Figure 12), unless capsular fixation is possible for the opposite haptic. The scleral flap is then closed with an absorbable suture

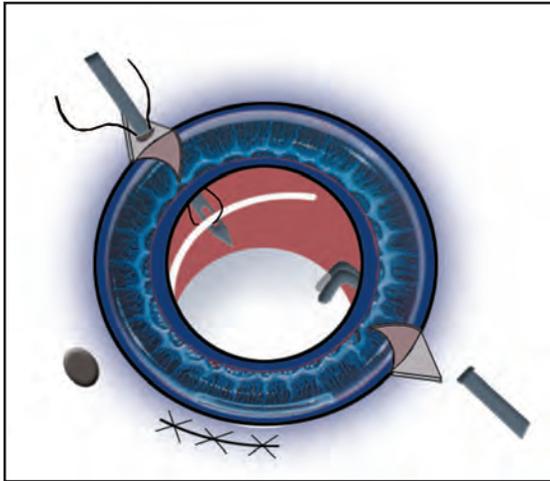


Figure 11: Suture connected to a needle passed through the scleral bed (Escalon Treck Medical). The IOL optic is grasped with the forceps and the haptic is guided through the loop. (Art from Jaypee - Highlights Medical Publishers).

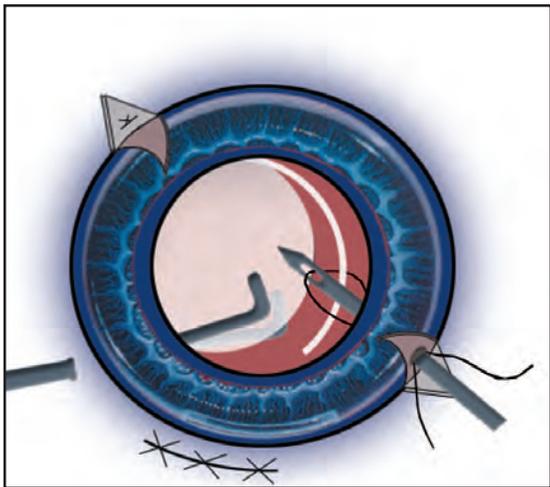


Figure 12: Opposed haptic is then guided through the loop. (Art from Jaypee - Highlights Medical Publishers).

and, if necessary, the vitrectomy is completed through the standard sclerotomies.

When the IOL has to be exchanged, appropriate optic size and haptic to haptic length are critical factors in the selection of an IOL. An optic of 6.5 mm to 7 mm is suggested. An IOL with an overall length of at least 12.5 mm will allow for adequate support in the ciliary sulcus. Using the larger lens is often helpful. However, if there is limited peripheral capsular or Soemmering-ring's support, we prefer to use several types of IOL especially designed for this purpose, which has a hole in the haptics to place the sutures. Once the dislocated IOL has been removed from the eye, a suture needle of Polypropylene is grasped, using a needle holder, and is passed through the bed of a scleral flap at 10-o'clock, 1 mm behind the limbus, and then it is guided to the bore of a bent 27 gauge needle inserted through the bed of the opposite scleral bed previously prepared (Figure 13). In this way the needle is guided outside the eye in a controlled manner. Then, the propylene suture is engaged in the pupillary space with an iris hook and brought outside the eye through the limbal incision (Figure 14). The ends of the suture are threaded through the holes located in the haptics, and are tightened (Figure 15). The IOL is then inserted in the sulcus, and the sutures are pulled, the needle is passed through the partial thickness of the scleral bed and the sutures are tightened; the procedure is repeated in the opposite scleral bed.

At the end of the procedure a careful inspection of the periphery to rule out retinal breaks is recommended.

Figure 13: The suture needle (right) is inserted, and is guided to the bore of a bent 27 gauge needle inserted through the opposite side. (Art from Jaypee - Highlights Medical Publishers).

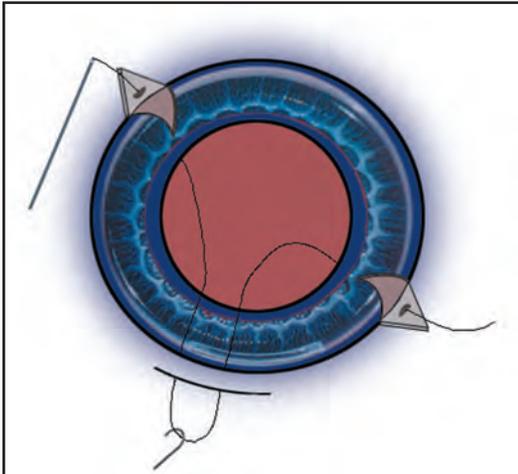
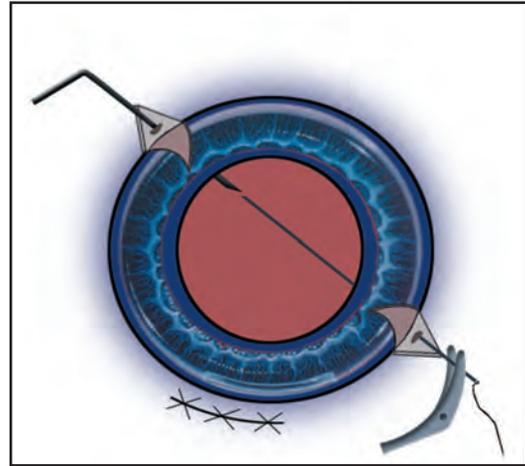
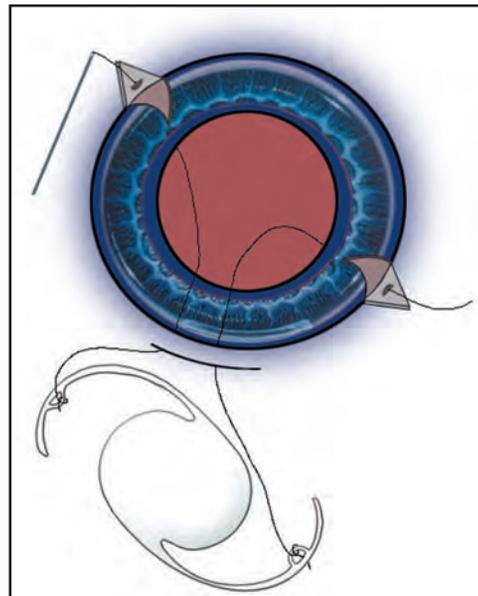


Figure 14: The suture is engaged, at the pupillary space, with an iris hook and brought outside the eye through the limbal incision. (Art from Jaypee - Highlights Medical Publishers).

Figure 15: The suture is cut, and the ends are threaded through the holes located in the haptics. (Art from Jaypee - Highlights Medical Publishers).





Complications

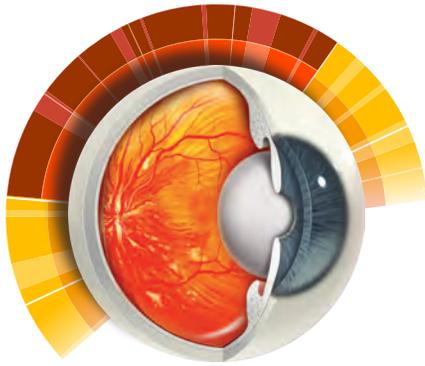
Contusion to the retina and retinal breaks may happen during surgical manipulations. Vitreous hemorrhage may occur if the major arterial circle of the iris is pierced inadvertently, during the maneuvers required to suture the IOL. Torque of the IOL may occur. Erosion of the sutures through the conjunctiva also has been reported. To melt the eroded sutures with the argon laser has been recommended. The sutures cannot be removed because the IOL haptics may not be fixed by a scar into place in the ciliary sulcus. Endophthalmitis due to bacterial migration along the transcleral suture has been described. The use of a partial thickness scleral flap to cover the suture knot reduces the risk for this complication. Retinal detachment occurs in about 2%.

Functional Results

The final visual acuity depends not only on pre-operative macular function, but also on complications of the original cataract surgery, such as cystoid macular edema and retinal detachment. With proper vitreo-retinal techniques, excellent visual results and a low complication rate is possible. A post-operative visual acuity of 20/40 or better has been reported between 50% and 94%.

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Retinal Complications After Refractive Surgery

J. FERNANDO AREVALO, MD, FACS

Introduction

The prevalence of myopia in the United States is said to be 25% to 46.4% of the adult population.^{1,2} In Asian populations these proportions may be much higher and in African and Pacific island groups, much lower. The market for refractive surgery has a very large potential for people with low (less than -5.00 diopters (D)) and moderate myopia (-5.01 to -10.00 D), and most patients fall into one of these two groups.²

Refractive surgery has been accepted for correcting ametropias, however this procedure may lead to complications. Several studies have described the retinal complications of refractive surgery since its early days, and procedures. Hofman et al³, Sanders et al⁴, and Feldman et al⁵ have described cases of retinal detachment (RD) after radial keratotomy. Rodriguez and Camacho⁶ reported 14 eyes (12 patients) which had either asymptomatic or symptomatic retinal breaks, subclinical and clinical rhegmatogenous RD, or both,⁷ after

Automated Lamellar Keratoplasty (ALK) and⁷ after radial keratotomy. Rodriguez et al⁷, Barraquer et al⁸, and Ripandelli et al⁹ have reported retinal detachments after clear-lens extraction for myopia correction. Ruiz-Moreno and associates¹⁰ reported the results of a clinically controlled study to investigate the rate of retinal detachment after implantation of phakic anterior chamber intraocular lenses. The implantation of a phakic anterior chamber intraocular lens as a correcting procedure for severe myopia was followed by a 4.8% incidence of retinal detachment.

Laser-assisted in situ keratomileusis (LASIK) has become one of the most popular options for the correction of low to moderate myopia worldwide.¹¹⁻¹² However, complications including undercorrections, overcorrections, flap displacement, epithelial ingrowth, flap melting, keratitis, retinal tears, retinal detachments, corneo-scleral perforations, retinal hemorrhages, macular holes, choroidal neovascular membranes, and irregular astigmatism have been reported.¹³⁻²⁵



The objective of this chapter is to review the retinal complications that may occur after refractive surgery with an emphasis on LASIK.

Retinal Detachments

Little has been reported in the literature regarding retinal detachments after LASIK. A Medline search reveals just a few studies.^{17, 20-24} Ozdamar et al²⁰ reported a case of bilateral retinal detachment associated with giant retinal tear after LASIK. Stulting and associates¹⁷ reported a case of rhegmatogenous retinal detachment after LASIK for the correction of myopia. Ruiz-Moreno and coworkers²¹ reported 4 retinal detachments (an incidence of 0.25%) in myopic eyes after LASIK and a mean best-corrected visual acuity of 20/45 after retinal surgery. Aras et al²² described 10 retinal detachments (an incidence of 0.22%) in myopic eyes after LASIK. Farah and coworkers²³ reported four eyes that had early rhegmatogenous retinal detachment within 3 months of LASIK for correction of high myopia. Although no cause-effect relationship between LASIK and retinal detachment can be stated from their study, the authors cases suggest that LASIK may be associated with retinal detachment, particularly in highly myopic eyes.

We have previously reported (Ramirez, and Arevalo et al, The Association for Research in Vision and Ophthalmology Annual Meeting, Fort Lauderdale, FL, May 1998 and Arevalo et al, American Academy of Ophthalmology Annual Meeting, New Orleans, Louisiana, November 1998) our two-year follow up of 29,916 eyes after LASIK for the correction of ametropias (myopes and hyperopes).

The incidence at 24-months of vitreo-retinal pathology in our study was 0.06% including 14 rhegmatogenous retinal detachments (RRD).²⁴ The incidence of RRD after LASIK in our previous studies ranges between 0.04% and 0.05%.²⁴⁻²⁵

For our latest data analysis (Arevalo JF. The Wilmer Eye Institute's Current Concepts in Ophthalmology-A Forum for Global Ophthalmic Innovators, Baltimore, MD, April 2007) we reviewed the medical records and obtained follow-up information on all patients in our files with rhegmatogenous retinal detachment (RRD) after LASIK for the correction of myopia between March 1996 to March 2004 at five institutions. A total of 83,938 LASIK procedures (eyes) were performed during the study period (8 years) by five experienced refractive surgeons. The mean age of the patients that had LASIK was 36 years (range: 16-60 years). Patients underwent surgical correction of myopia ranging from -0.75 to -29.00 D (mean: -6.19 D). Patients were scheduled to be seen during the first postoperative day, at 3 months, at 12 months, and yearly thereafter. Patients were followed for a mean of 65 months after LASIK (range: 6-84 months).

Five vitreo-retinal surgeons and 40 eyes (34 patients) that developed RRD after LASIK for the correction of myopia participated in the study (Figures 1 and 2). The clinical findings, frequency of RRD after LASIK, characteristics (fundus drawings of the 40 eyes were evaluated), and surgical outcomes of 38 eyes (two patients refused surgery) are presented. Patients with RRD after LASIK were included in the study independent on the length of follow-up.

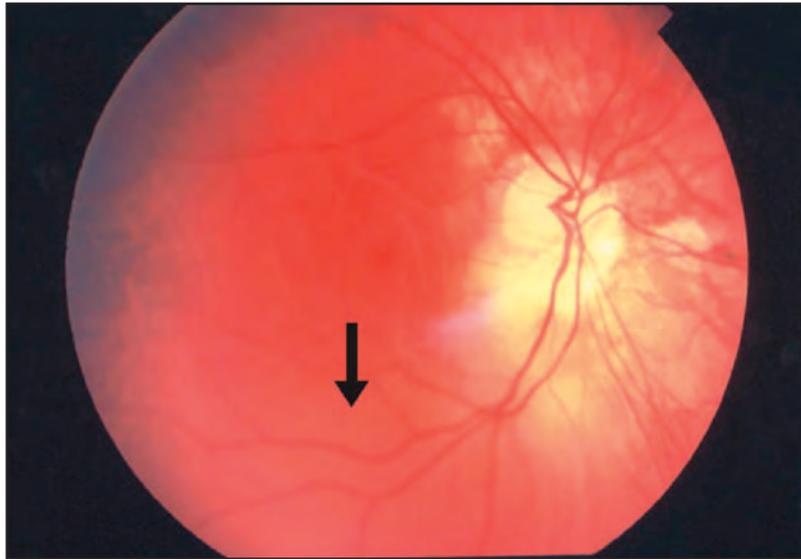


Figure 1: Fundus photograph of a subtotal infero-temporal retinal detachment (macula off) after laser in situ keratomileusis.

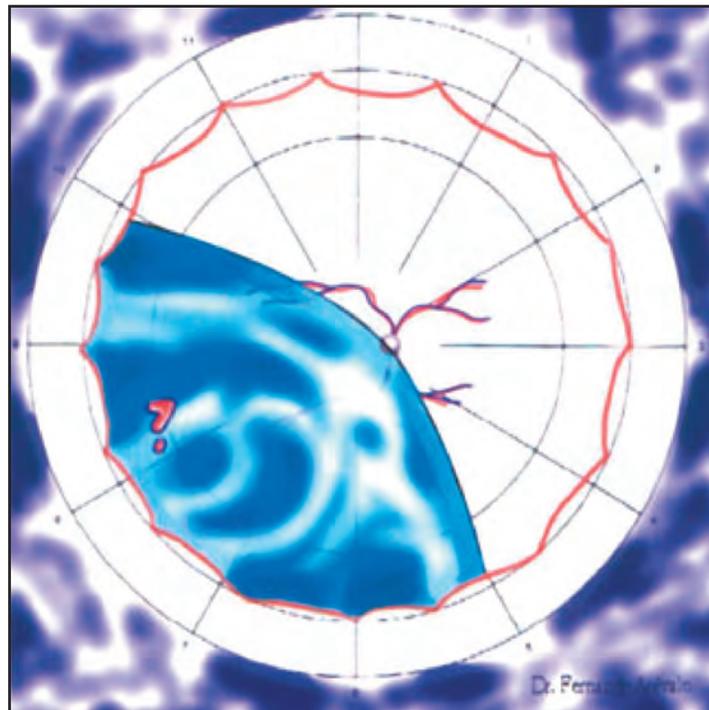


Figure 2: Retinal drawing of a subtotal infero-temporal retinal detachment (macula off), partial posterior vitreous detachment, a horseshoe retinal tear at 8 o'clock, and a retinal hole at the same location.



Final visual acuity (VA) was defined as the best corrected visual acuity at last follow-up examination, ranging from 3 to 46 months (mean: 26 months) after vitreo-retinal surgery to repair RRD after LASIK. Laser in situ keratomileusis was performed on patients with no history of prior refractive surgery, keratoconus, prior cataract surgery, proliferative diabetic retinopathy, or collagen vascular disease. Preoperative examinations included a very thorough dilated funduscopy with scleral depression and treatment of any retinal lesion predisposing for the development of a RRD.

We found forty eyes (34 patients) that developed RRD after LASIK for the correction of myopia. Our 34 patients had an average age of 37.8 (16-60) years old, and 66.6% were male. In our series 9% of eyes that developed a RRD had some kind of enhancement after LASIK. No patient had a history of any other ocular surgery after LASIK. The frequency of rhegmatogenous retinal detachments determined in our study is 0.04% (40/83,938).

Rhegmatogenous retinal detachments occurred between 12 days and 60 months (mean: 16.3 months) after LASIK. Eyes that developed a RRD had from -1.50 to -16.00 D of myopia (mean: -8.75 D) before LASIK. Retinal detachments were managed with vitrectomy, cryoretinopexy, scleral buckling, argon laser retinopexy, and pneumatic retinopexy techniques. In cases that developed a retinal detachment, a pars plana vitrectomy was performed using an Accurus (Alcon Laboratories, Fort Worth, TX) or a Millennium (Bausch & Lomb Surgical, Claremont, CA) vitrectomy system. Three 1.0 mm-wide sclerotomies were made using a microvitreous (MVR) blade from 2.5 to 3.5 mm posterior to the limbus. The infusion line

was sutured in the infero-temporal quadrant. After vitrectomy, sulfur hexafluoride (SF_6) gas was used or 5,000 centistokes (cs) silicone oil (Richard-James, INC., Peabody, MA). A scleral buckling procedure was performed using a circumferential scleral band (Mira 240; Mira, Waltham, MA) sutured with the posterior border located 12 mm posterior to the limbus, and adding any necessary segmental sponges (Mira, Waltham, MA) when needed. Cryoretinopexy was performed using a CTU Ophthalmic Cryo Unit (Keeler, London, England). Argon laser retinopexy was performed using an HGM's PC EDO argon (only green) laser (HGM, Salt Lake City, Utah) using the indirect delivery system (LIO). Pneumatic retinopexy was performed using the same argon laser (PC EDO) with LIO and sulfur hexafluoride (SF_6) gas.

Vitreo-retinal surgery to repair RRD after LASIK was performed at a mean of 56 days (range: 1 day to 18 months) after the onset of visual symptoms. The mean follow up after retinal surgery was 26 months (range: 3 to 46 months) and 38.7% of the 38 eyes (two patients refused surgery) had a final best corrected visual acuity (VA) of 20/40 or better. Final VA was better than 20/200 in 77.4% of eyes. Poor VA (20/200 or worse) occurred in 22.6% of eyes. Reasons for poor VA included the development of proliferative vitreo-retinopathy (PVR), epiretinal membrane, chronicity of RRD, new breaks, displaced corneal flap, and cataract.

Final VA after RRD surgery improved 2 lines or more in 51.6% of eyes. The anatomic success at final follow-up with one surgery was 87.1%. Three eyes required from 1 to 3 reoperations with pars plana vitrectomy and silicone oil injection (Figure 3) and one eye

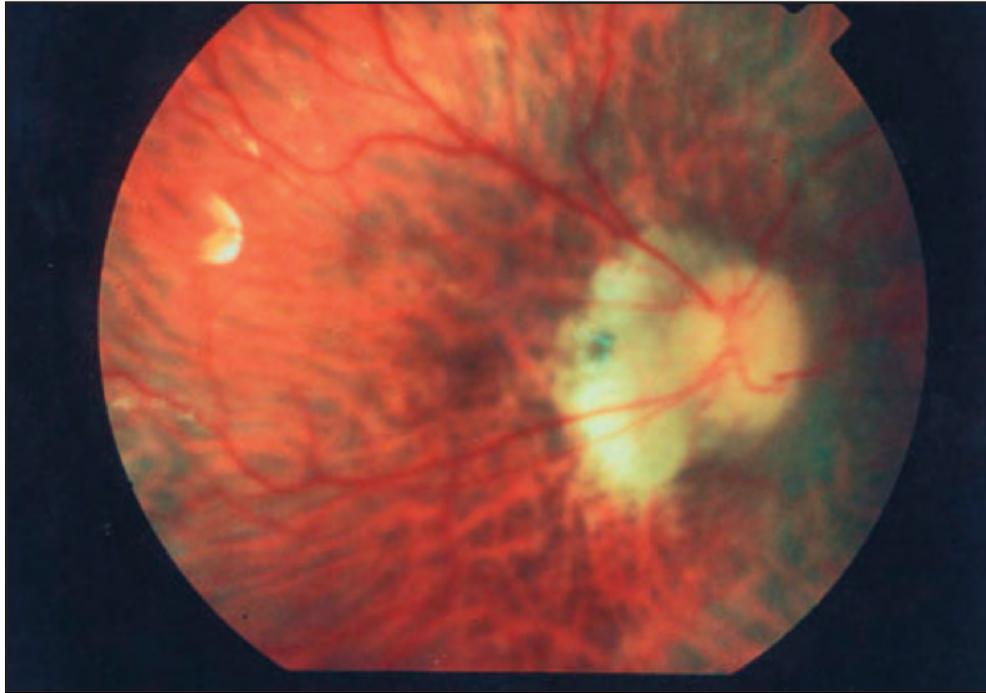


Figure 3: Postoperative fundus photograph of a myopic eye that developed a rhegmatogenous retinal detachment with proliferative vitreoretinopathy (PVR) after laser in situ keratomileusis. Vitrectomy and silicone oil injection was successfully performed.

required argon laser retinopexy to seal new retinal breaks. The anatomic success at final follow-up including reoperations was 90.3%. Information regarding VA after LASIK and before the development of RRD was available in 30 eyes, 45.8% of eyes lost 2 or more lines of VA.

Retinal Breaks, Posterior Vitreous Detachment, and Lattice Degeneration

Fundus drawings of the 40 eyes were evaluated (Figure 2). The mean number of retinal breaks per RRD was 4.3 (range: 0-40),

including 98 holes, 41 horseshoe tears, two retinal dialysis, and one giant retinal tear. In 71.1% of cases retinal breaks were located temporally. The vitreous status was available from 33 of our cases, and 62.9% had posterior vitreous detachment (PVD), and 22.5% of our RRD cases had a retinal break associated to lattice degeneration. In 19.3% of our cases RRD was associated with proliferative vitreoretinopathy (PVR) grade C.

The long interval between the onset of symptoms and RRD surgery may be responsible for some of the factors (including a 19.3% rate of PVR) that contributed to poor final VA in more than 20% of our cases. In some of our patients there may have been some delay in



the referral to the vitreo-retinal specialist due to a belief that the visual symptoms were related to a refractive or corneal problem after LASIK. In addition, other factors related to high myopia (including myopic degeneration and amblyopia) might also influence the final functional results regardless of our high anatomic success rate.

Macular Hemorrhage and Choroidal Neovascular Membranes

Few reports have been published regarding macular hemorrhage after LASIK. Kim and Jung²⁶ reported one eye that lost greater than two lines of pre-operative best-corrected vision due to macular hemorrhage. Luna et al²⁷ have reported a case of bilateral macular hemorrhage after LASIK. One day after surgery the patient's uncorrected visual acuity was in the 20/50 range and by 17 days after surgery his visual acuity had declined to 20/200 range. Fundus examination showed multifocal subretinal macular and posterior pole hemorrhages. Fluorescein angiography showed some macular lesions compatible with lacquer cracks.

Only a few studies can be found regarding choroidal neovascular membranes after refractive surgery. We have described the first case of a choroidal neovascular membrane (CNV) that presented after LASIK.²⁴ A 48 year-old Hispanic hyperopic (+3.50 D OD and +4.00 D OS) man was seen on December of 1997

at our institution because of visual loss OS two years after a LASIK procedure. On examination, visual acuity was 20/400, and biomicroscopy was unremarkable. Dilated funduscopy and fluorescein angiography showed a juxtafoveal CNVM with sub-retinal fluid (Figure 4-A). A pars plana vitrectomy and a temporal retinotomy were performed to remove the CNVM from the sub-retinal space and air was instilled into the vitreous cavity. Topical steroids and cycloplegics were prescribed. Eight months later his visual acuity OS was counts fingers and funduscopy showed a juxtafoveal retinal pigment epithelium defect (Figure 4-B).

Ruiz-Moreno et al²⁸⁻²⁹ have reported an incidence of 0.1% CNV after LASIK and one case after photorefractive keratectomy (1/5936). The incidence seems to be very low, however the appearance and treatment of CNV was followed by a significant decrease of visual acuity. Choroidal neovascularization is related to myopia itself and its incidence varies from 4 to 11% in patients with high myopia. In addition, lacquer cracks have been found to be associated with CNV in up to 82% of cases with myopia.²⁸ Theoretically, when a break in Bruch's membrane occurs, it allows invasion of the neovascular complex under the retina. The increase in intraocular pressure (IOP) to levels over 60 mm Hg during suction with the microkeratome suction ring up to 4 mm posterior to the limbus may exert traction and compression posteriorly. In addition, we have to consider that the excimer laser is responsible for a shock wave that is transmitted to the eye. These mechanisms may open the gap in Bruch's membrane

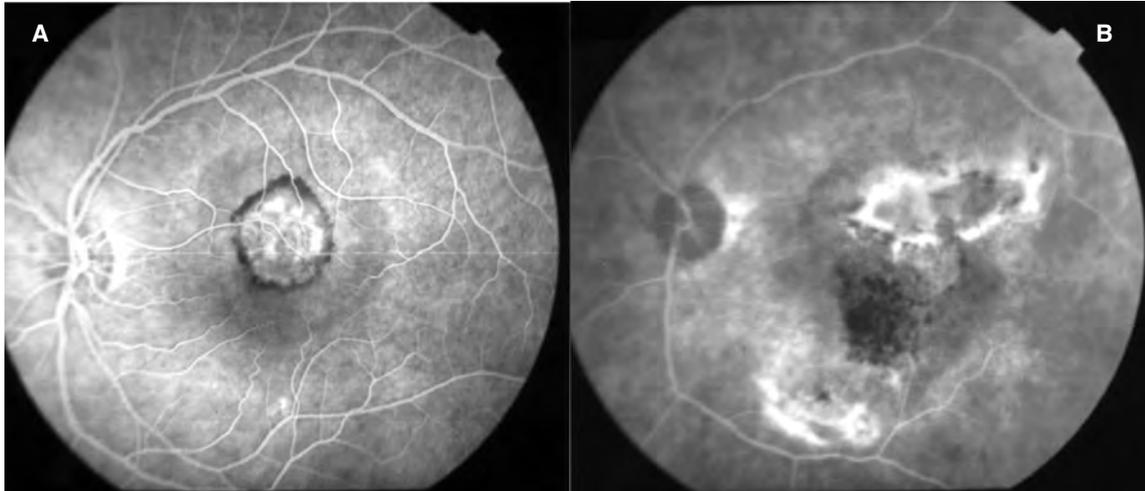


Figure 4 A-B: A) Fluorescein angiography showed a juxtafoveal choroidal neovascular membrane (CNV) with sub-retinal fluid and cystoid macular edema. B) Fluorescein angiography after CNV surgical removal shows retinal pigment epithelium defect (Fig. 4A reprinted with permission from Arevalo et al. *Incidence of vitreo-retinal pathologic conditions 24 months after laser-assisted in situ keratomileusis (LASIK)*. *Ophthalmology* 2000;107:258-262).

even more. We believe that in patients with high myopia and lacquer cracks (Figure 5), LASIK should be considered contraindicated and some other method of refractive surgery offered (i.e. phakic intraocular lens).

Macular Hole

Arevalo et al³⁰ described nineteen patients (20 eyes) who developed macular hole after undergoing bilateral LASIK for the correction



Figure 5: Fundus photograph of a highly myopic eye with lacquer cracks, LASIK should be considered contraindicated and some other method of refractive surgery offered (i.e. phakic intraocular lens) in these cases.

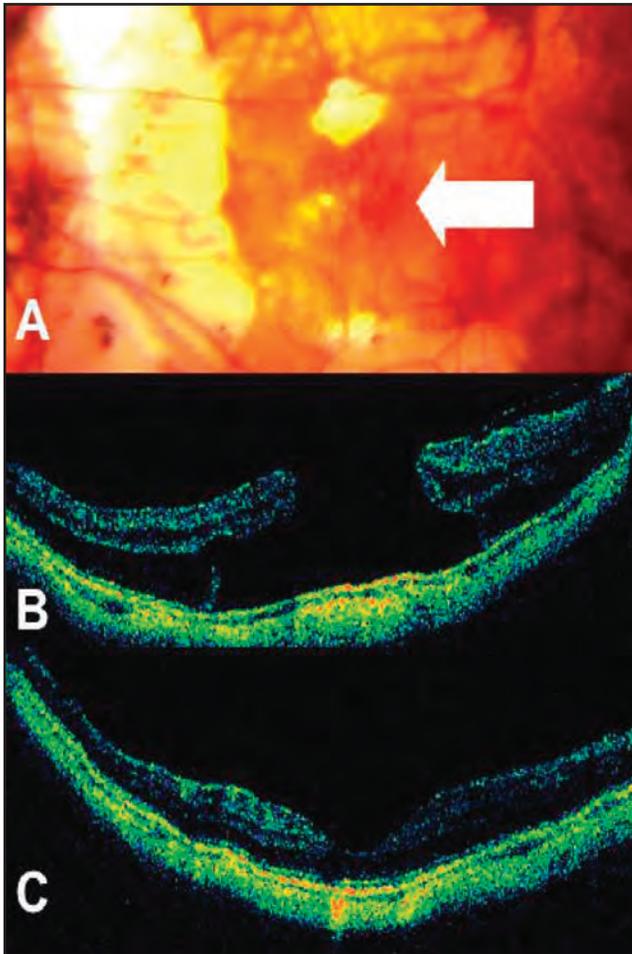


Figure 6A-C: A) Retinal examination revealed a stage 4 macular hole (arrow) in the left eye associated with a posterior pole retinal detachment, and a best-corrected visual acuity (BCVA) of counting fingers. B) Optical coherence tomography (OCT) image showing features of both foveal retinal detachment and retinoschisis. C) OCT after vitrectomy reveals a closed macular hole with a BCVA of 20/150 (Reprinted with permission from Arevalo et al. *Vitreoretinal surgery for macular hole after laser assisted in situ keratomileusis for the correction of myopia. Br J Ophthalmol* 2005;89:1423-6).

of myopia. The macular hole formed at a mean of 12.1 months after LASIK. In 60% of cases the macular hole developed ≤ 6 months after LASIK, and in 30% of cases the macular hole developed one year or more after LASIK. Eighteen out of 19 (94.7%) patients were female. Mean age was 46 years old. All eyes were myopic (mean: -8.9 D). Posterior vitreous detachment (PVD) was not present before and was documented after LASIK on 55% of eyes. A vitrectomy closed the macular hole on the fourteen eyes that underwent

surgical management with an improvement on final best-corrected visual acuity on 13 out of 14 (92.8%) patients (Figure 6). The 20 eyes with full-thickness macular hole after LASIK reflect an incidence of 0.03% (20/55,458). The authors concluded that a macular hole may infrequently develop after LASIK for the correction of myopia, and that vitreoretinal surgery can be successful in restoring vision for most myopic eyes with a macular hole after LASIK.

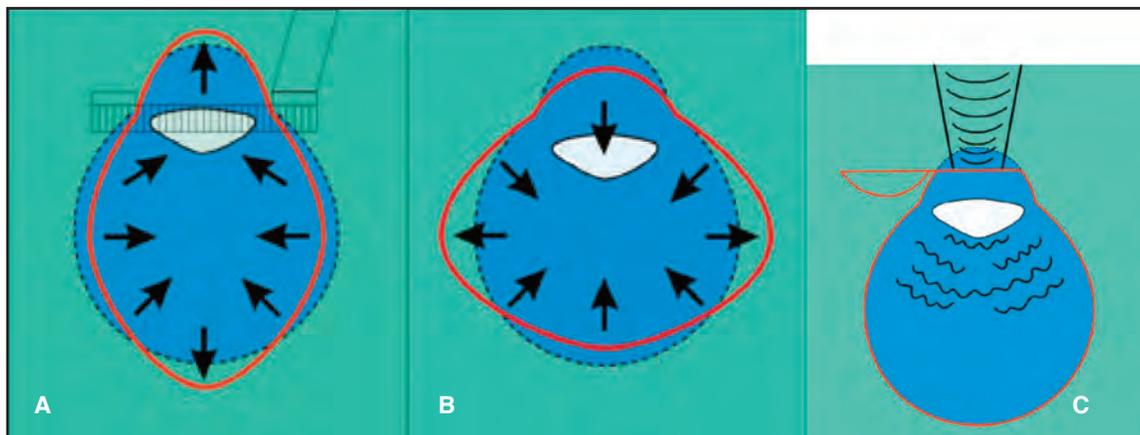


Figure 7A-C: The following changes may cause acute vitreo-retinal traction at the vitreous base and posterior pole. A) When the suction ring is in place, the eye deforms along the anterior-posterior axis and the diameter of the globe may increase. At the same time, because the eye is a closed system, the eye must contract along the horizontal axis and equatorial diameter may decrease. B) When the suction stops and the suction ring is released, decompression leads to a dynamic overshoot with equatorial elongation and anterior-posterior contraction. C) In addition, the excimer laser-induced shock wave may play a role in the development of posterior vitreous detachment (*Reprinted with permission from Arevalo et al. Rhegmatogenous retinal detachment in myopic eyes after laser in situ keratomileusis. Frequency, characteristics, and mechanism. J Cataract*

How could the excimer laser, or the microkeratome, cause a macular hole? What is the pathophysiology? When the suction ring induces an increase in IOP and then is suddenly released, the anterior segment is rapidly drawn into a vacuum chamber with its shape changed rapidly, and all structures posterior to the suction ring are also compressed and decompressed in sequence. This type of “trauma” is in some ways analogous to what happens in a closed eye injury. A mechanism for development of peripheral retinal tears or macular disease could be anterior-posterior compression and expansion. The eye elongates along the anterior-posterior axis and the diameter of the globe may increase. At the same time, because the eye is a closed system, the eye is constricted in the equatorial plane (Figure 7A). As the anterior segment is drawn into a vacuum, the lens may be displaced forward along with the

anterior hyaloid. This might accelerate vitreous detachment or cause traction at the vitreous base. When the suction is suddenly released, decompression leads to a dynamic overshoot with equatorial expansion and shortening in the anterior-posterior dimension (Figure 7B). These events may cause acute vitreo-retinal traction at the vitreous base and posterior pole.

In addition, when the excimer laser light ablates tissue, energy is released anteriorly as a plume of ablated tissue and is thrown into the air in front of the cornea. Certainly such a powerful force might also be associated with backward force into the vitreous. Posteriorly, energy is transmitted in the form of a shockwave (Figure 7C). The effect of such shockwaves and posteriorly radiated energy on the vitreous integrity is unknown.



Corneo-Scleral Perforations

In our series²⁴, two eyes had suffered corneo-scleral perforations with the surgical microkeratome when a corneal flap was being performed (one of them developed a vitreous hemorrhage and the other one later developed a retinal detachment).

A 24 year-old Hispanic myopic (-5.00 D OD and -4.25 D OS) woman was seen on August of 1995 at our institution because of visual loss OD immediately following a LASIK procedure. According to the refractive surgeon, he had omitted to place a spacing plate into the microkeratome when a corneal flap was being performed. An ocular perforation occurred with corneal and iris wounds, loss of the crystalline lens, vitreous loss, and the development of vitreous hemorrhage. We performed a thorough anterior vitrectomy and sutured the corneal and iris wounds with 10-0 nylon. Oral and topical steroids were prescribed. Thirteen months later her visual acuity was 20/25-1 with a contact lens.

In the second case, a 38 year-old Hispanic myopic (-20.00 D OD and -15.00 D OS) woman was seen on May of 1997 at our institution because of visual loss OS following a LASIK procedure. According to the refractive surgeon, a corneal perforation had occurred with the microkeratome when a corneal flap was being performed. She had undergone crystalline lens remnant aspiration and an anterior vitrectomy one week later. On examination, a sutured (10-0 nylon) corneal wound with Descemet folds is seen on biomicroscopy (Figure 8A). Dilated funduscopy did not show details of the retina due to opacities of the media. Di-

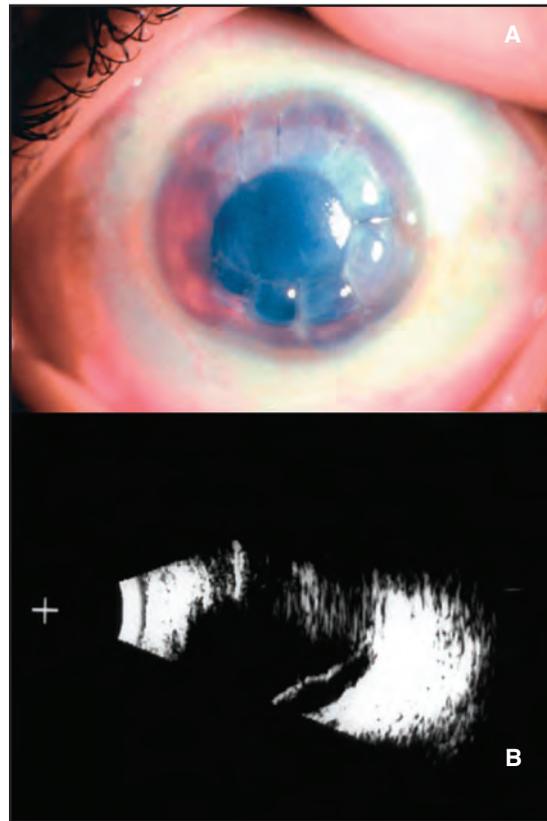


Figure 8 A-B: A) Sutured (10-0 nylon) corneal wound with Descemet folds is seen on biomicroscopy. B) Diagnostic B-scan ultrasound shows an inferior retinal detachment (Reprinted with permission from Arevalo et al. *Incidence of vitreo-retinal pathologic conditions 24 months after laser-assisted in situ keratomileusis (LASIK)*. *Ophthalmology* 2000;107:258-262).

agnostic B-scan ultrasound showed an inferior retinal detachment (Figure 8B). A vitrectomy was performed with a 360° circumferential scleral band, endolaser, and SF₆. Topical steroids and cycloplegics were prescribed. Three months later she developed a retinal tear in the fellow eye (also treated with LASIK) which was managed with an argon laser retinopexy. Six months later her visual acuity OS was hand motions due

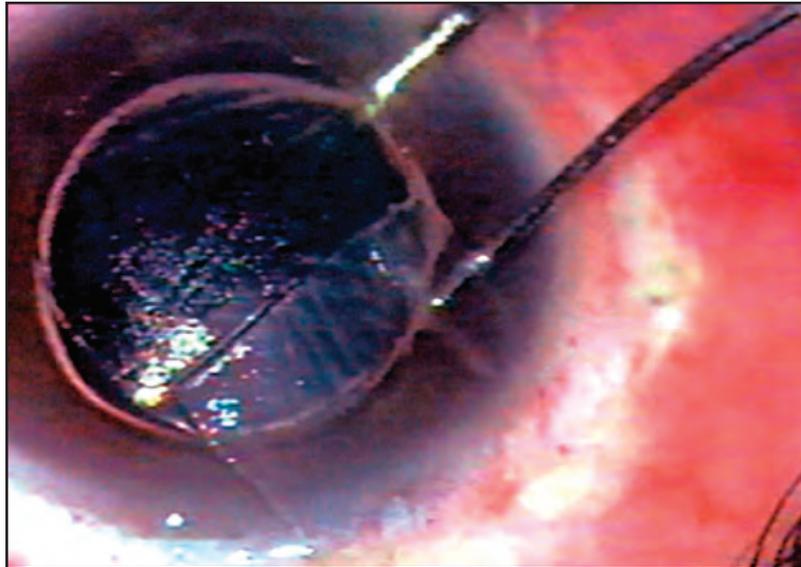


Figure 9: In one of our cases, a dislocated corneal flap occurred from corneal epithelial debridement during vitrectomy 69 months after laser in situ keratomileusis.

to corneal scarring and a recurrent inferior rhegmatogenous retinal detachment.

Some cases of LASIK induced corneal perforation have been treated by applying a therapeutic soft contact lens with topical antibiotics, oral carbonic anhydrase inhibitors, and eye patching. However, we believe that it is important to mention that LASIK-induced corneal perforations can be very severe and sutures may be necessary. In addition, severe cases may be associated to posterior segment damage as demonstrated in our report.²⁴ The incidence of vitreo-retinal complications (vitreous hemorrhage and retinal detachment after corneo-scleral perforations) during LASIK determined in our study is 0.006% (2/29,916).

We recommend that refractive surgeons be meticulous in properly assembling the

microkeratome to create a corneal flap during LASIK. The use of currently available disposable microkeratomers may help to avoid this complication in the future.

Displacement of Corneal Cap During Vitrectomy

In one of our cases, a dislocated corneal flap (Figure 9) occurred with corneal epithelial debridement during vitrectomy 69 months after LASIK. A similar case has been previously reported by Chaudhry and Smiddy³¹. Their case underwent vitreous surgery only 4 months after LASIK.

Displacement of a corneal flap after LASIK is a potentially serious complication. Possibilities include losing the cap, epithelial



ingrowth, interface particles, and striae in the flap (trauma to the flap may affect the final refractive status). Displacement of the corneal flap has been described after corneal epithelial debridement during a scleral buckling procedure, and vitrectomy.

Recommendations for vitreo-retinal surgeons when treating an eye with a history of LASIK include avoiding debridement of the corneal epithelium. However, if it is necessary, start corneal debridement nasally and advance temporally (most cases have a nasal hinge). If a displaced corneal flap occurs, initial management includes repositioning of the flap, followed by patching and topical steroids. Refractory cases may require suture fixation. A bandage contact lens may be useful if striae develop. If striae persist, it is an indication to elevate and reposition the flap.

Final Considerations

Laser-assisted in situ keratomileusis (LASIK) has become the most popular option for the correction of low to moderate ametropias worldwide. The number of patients who have had LASIK is not accurately known. In the US, the market estimate for LASIK procedures is 900,000 per year. We estimate that in Latin-America, LASIK is done in 0.06% of the population per year. At least 80% of those cases are myopes, typically from -0.50 to -10.00 diopters (D). Patients with higher degrees of myopia tend to be corrected now with the aid of phakic intraocular lens or phacorefractive surgery to avoid excessive ablation of the corneal bed by the excimer laser.

The incidence of rhegmatogenous retinal detachment (RRD) in myopes in general is 1 to 3%.³² There is a relationship between the severity of myopia and the frequency of RRD.³³⁻³⁵ Ogawa et al analyzed 1,116 RRD cases and found that myopia was present in 82.16% of them. In myopia higher than -15.00 D the frequency of RRD was 68.6 times higher than for patients with hyperopia.³³ In most myopes there is an axial component, and vitreous modifications and peripheral fundus abnormalities in myopic eyes are the major factors that predispose to RRD.³⁴ The Eye Disease Case-Control Study Group reported that an eye with a spherical equivalent refractive error of -1.00 to -3.00 D had a fourfold increased risk of retinal detachment compared with a non-myopic eye; if the refractive error was greater than -3.00 D, the risk was increased 10-fold.³⁵

Is there a cause-effect relationship between LASIK and the development of retinal breaks and detachment, and between LASIK and exacerbation of macular changes associated with myopia? How do we account for the development of vitreo-retinal disease after LASIK? It is important to first state that there is little hard data with which to even attempt to determine if there is any causative relationship. Myopes undergo LASIK in ever increasing numbers and myopes are predisposed to retinal detachment as well as macular hemorrhage and other macular pathologies. It is possible that these abnormalities or exacerbation of these conditions are associated with the LASIK procedure itself. However, they may have occurred anyway. Unfortunately, it is very difficult to do a controlled study.



The basic LASIK procedure is based upon concepts and patients operated on by Barraquer.³⁶ During the procedure, a lamellar corneal flap must be made to allow intrastromal ablation by the excimer laser beam. In order to obtain a consistent flap of the optimal thickness, the cornea is stabilized by a suction ring which is placed just behind the limbus and which sucks the anterior segment into a vacuum device firming the eye and the cornea. This device, the suction ring, has not changed in basic principle in the last 35 years. The following sequence of events might occur during the LASIK procedure. When the suction ring induces an increase in IOP (65 mmHg) and after that it is suddenly released, the anterior segment is rapidly drawn into a vacuum chamber with its shape changed rapidly, and all structures posterior to the suction ring are also compressed and decompressed in sequence. This type of "trauma" is in some ways analogous to what happens in a closed eye injury³⁷⁻³⁸ ("closed-suction injury"). A mechanism for development of peripheral retinal tears or macular disease could be anterior-posterior compression and expansion. The eye elongates along the anterior-posterior axis and the diameter of the globe may increase. At the same time, because the eye is a closed system, the eye is constricted in the equatorial plane (Figure 7A). As the anterior segment is drawn into a vacuum, the lens may be displaced forward along with the anterior hyaloid. This might accelerate vitreous detachment or cause traction at the vitreous base. When the suction suddenly is released, decompression leads to a dynamic overshoot with equatorial expansion and shortening in the anterior-posterior dimension (Figure 7B). These events may cause acute vitreo-retinal traction at the vitreous base and posterior pole.

Lens displacement could be responsible for cases of cataracts after LASIK. During compression there is traction posteriorly that may be responsible for the anecdotal reports of macular holes and macular hemorrhages. It is possible that there is deformation and traction near the vitreous base, which lies just posterior to the suction ring, this can be a cause of retinal breaks. We have measured the marks left immediately after the suction ring is applied in the sclera and its posterior border is at a mean of 4-mm posterior to the limbus. The elevation in IOP as well as the potential for deformation of the globe in the macula might also lead to exacerbation of macular pathology that can be present in high myopes such as defects in Bruch's membrane (lacquer cracks).

Another potential source of damage to the vitreous and retina is from the pulsed energy applied to the cornea (Figure 7C). The excimer laser light ablates tissue; energy is released anteriorly as a plume of ablated tissue and is thrown into the air in front of the cornea. In addition, it has been reported that particulate matter was ejected from the cornea for up to 18 inches. Certainly such a powerful force might also be associated with backwards force into the vitreous. Hahn et al showed that most of the ablation particles seen to be launched in the air are water spherules. The particle diameter is 100-800 microns.³⁹ Posteriorly, energy is transmitted in the form of a shockwave on the order of 10 atmospheres of pressure (Seiler and Krueger, unpublished observations). The effect of shockwaves and posteriorly-radiated energy on the vitreous integrity is unknown.

The incidence of vitreo-retinal pathology after LASIK in our studies was 0.06% (annual incidence 0.02%).²⁴ This number is much



lower than the incidence of RRD in myopes in general.³² This finding may be explained by the fact that refractive surgery patients in the institutions involved underwent preoperative examinations including a very thorough dilated indirect funduscopy with scleral depression and treatment of any peripheral retinal lesion predisposing for the development of a RRD before LASIK. In this study extensive lattice degeneration, flap tears, atrophic holes, and retinal tufts were prophylactically treated regardless of symptoms. Such indication is justified by the fact that vitreo-retinal surgery causes changes in corneal shape thus damaging the refractive surgeon's results as demonstrated by Azar-Arevalo and Arevalo.⁴⁰ We suggest that cryopexy, argon laser retinopexy, pneumatic retinopexy or small-gauge (25 or 23-gauge) vitrectomy without a scleral band be performed when appropriate because they tend not to change the shape or length of the globe. Another option in case of scleral buckling procedures is to remove the exoplänts early, as suggested by Rodriguez and Camacho⁶, after being sure that all breaks have sealed and that no retinal detachment is present anywhere in the fundus.

We cannot determine whether treatment prophylactically is indicated. At the current time it is not possible to scientifically determine whether peripheral retinal lesions should be treated in a way different from standard practice just because a patient is to undergo LASIK. Most practitioners suggest that patients scheduled for LASIK be carefully examined with indirect ophthalmoscopy and scleral depression under pupillary dilatation to detect any myopic peripheral lesion that requires

treatment before LASIK is performed. One could argue that this is prudent in myopes whether or not they undergo LASIK; given the potential of the procedure to exacerbate pre-existing pathology, it might be wise to treat such pathology more aggressively.

Another important factor to take into consideration when we evaluate our state of knowledge in this area is duration of follow up. It is reasonable to expect that the incidence of RRD in the initial cohort of patients that had LASIK will rise with time. It is possible that LASIK induced trauma might accelerate vitreous liquefaction and that over the years these patients might have a higher incidence of retinal detachments and other vitreo-retinal problems. It is equally likely that with the current practice patterns, we ophthalmologist would be unaware of this.

Macular diseases may be a relative contraindication to LASIK. Patients with high myopia and lacquer cracks in the macula are at high risk to develop macular hemorrhage or CNV after the intraocular pressure is raised with the suction ring during the procedure. Patients with angioid streaks and traumatic choroidal ruptures are in the same category of risk. Stage 1 macular holes may progress due to traction in the posterior pole during LASIK. In addition, eyes that are at risk of needing vitreoretinal surgery in the future have a relative contraindication to LASIK. On the other hand, in eyes with stable macular disease (scars), LASIK may be performed depending on the refractive surgeon's criteria if the patient is aware and accepts his visual acuity limitations.



Summary

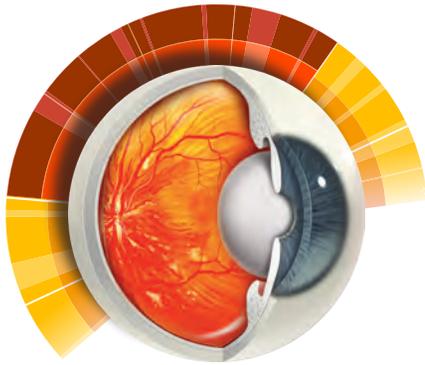
Serious complications after LASIK are infrequent. It is very important to inform patients that LASIK only corrects the refractive aspect of myopia. Vitreoretinal complications in these eyes will occur and only careful and large prospective studies in patients can determine if the procedure exacerbates myopic pathology. Such studies will need to be performed using careful prospective examinations including determination of risk factors, echography of the vitreous, indirect ophthalmoscopy and scleral depression and possible photography and angiography of the macula region to determine whether the LASIK procedure itself can exacerbate pathologic changes in the myopic eye. In addition, our studies show that results may be not as good as expected after RRD surgery. Reasons for poor VA include the development of epiretinal membrane, proliferative vitreo-retinopathy, chronicity of RRD, new retinal breaks, and cataract formation. Final VA may be limited by myopic degeneration, amblyopia, or delayed referral to a vitreo-retinal specialist.

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31

Management of Intraocular Hemorrhage and Other Complications

GEORGE B. PETERS III, M.D., M.B.A.

GEORGE K. ASDOURIAN, M.D.

LINDA STEIN, M.S.

SHALESH KAUSHAL, M.D., PH.D.

Introduction

This chapter discusses intraocular hemorrhage of interest to the retina specialist and posterior-segment surgeon, with a focus on vitreous hemorrhage. Issues related to hyphema and other anterior segment hemorrhages will not be discussed. Additionally, small hemorrhages within the retina, most commonly seen with diabetes mellitus and systemic hypertension as well as a myriad of other less commonly associated disorders, will not be addressed, although technically these do qualify as intraocular hemorrhages. Subretinal and suprachoroidal hemorrhages, which are relatively uncommon, also are not covered in this chapter.

A vitreous hemorrhage is one of the most common disorders presenting to a retina practice. Its underlying etiology is variable although most often related to proliferative

diabetic retinopathy. Other pathologies in the differential diagnosis for vitreous hemorrhage include vascular occlusive disease, retinal breaks or tears, a posterior vitreous detachment, exudative macular degeneration, as well as rare neoplasia. Additional uncommon causes of vitreous hemorrhage include trauma, radiation retinopathy, retinopathies secondary to hemoglobinopathies and inflammation. Table 1 lists the etiologies of vitreous hemorrhages, in order of relative incidence.

First, we will discuss the management of patients with vitreous hemorrhage and then discuss the underlying disease states that are the primary pathologies responsible for vitreous hemorrhages. Although this order of presentation may seem backwards, often vitreous hemorrhage requires management without certitude of the underlying pathology responsible, which may be unclear or presumptive (e.g., in the case of diabetes mellitus). Fortunately, the clear media of



Table 1
Etiology of Vitreous Hemorrhage by Mechanism and Relative Incidence

Incidence

- i- Retinal Neovascularization
 - Diabetic Retinopathy
 - Other Retinal Vascular Occlusive Disease
 - Central Retinal Vein Occlusion
 - Branch Retinal Vein Occlusion
 - Central Retinal Artery Occlusion
 - Branch Retinal Arteriole Occlusion
 - Retinopathy associated with Hemoglobinopathy
 - Peripheral Vascular Occlusive Disease
 - Vasculitis (Phlebitis, Arteritis or Both)
 - Posterior or Intermediate Uveitis
 - Radiation Retinopathy
- ii- Pathology of the Vitreo-Retinal Interface
 - Peripheral Retinal Tears/Breaks
 - Posterior Vitreous Detachment
- iii- Choroidal Neovascularization
 - Exudative Age-related Macular Degeneration
 - Peripheral Choroidal Neovascularization
 - Choroidal Neovascularization from Other Disorders
- iv- Neoplasia
- v- Trauma

intraocular tissues allows the ophthalmologist to often see intraocular pathology directly. Thus ophthalmologists commonly are able to eliminate (or mitigate) the uncertainty of diagnosis much of the time. The patient history, diagnostic testing, and to a lesser extent the physical examination are more critical in managing vitreous hemorrhages than for other ocular conditions that can be visualized directly.

Patient History

Management of a vitreous hemorrhage generally requires more emphasis on the

patient history than in patients with other retinal diseases. For vitreous hemorrhages, the time from onset of symptoms to presentation is typically a matter of hours or days, since hemorrhages are typically, though not exclusively, dramatically symptomatic. With large vitreous hemorrhages, symptoms typically occur suddenly with significant loss of vision; these hemorrhages also typically obscure the view of the examiner as well as the patient. With smaller vitreous hemorrhages, symptoms of black floaters can occur which commonly appear to rise from inferior to superior visual space, secondary to the inverted real image projected on the

retina. Movement of floaters may be reported as resembling air bubbles underwater as in an aquarium, owing to the blood's circuitous track in the irregularly syneretic vitreous body. Some patients report symptoms as a myriad of small objects obscuring vision in the affected eye, or looking through a screen door or window (Figure 1).

Pain is universally absent with the exception of patients for whom the etiology is trauma, which would be generally obvious from the history. A history of any known ophthalmic disease should be elicited. Review of the patient's medical history may include a pre-existing ocular disease such as recent ophthalmic surgery, diabetic retinopathy or

ocular neoplasm. Often, however, no such history is reported, with the common exception of diabetes mellitus. In much of the industrialized world, undiagnosed diabetes mellitus is relatively unlikely if effective widespread screening has been conducted. However, in the United States routine screening for diabetes mellitus is not extensive due to high costs, and in much of the developing world screening is generally unavailable. In any case, eliciting a history of diabetes mellitus specifically is critical. If a patient presenting with a vitreous hemorrhage with no known predisposing risk factor responds that he or she does not have diabetes mellitus, follow-up questioning regarding a family history of diabetes mellitus and the date and method

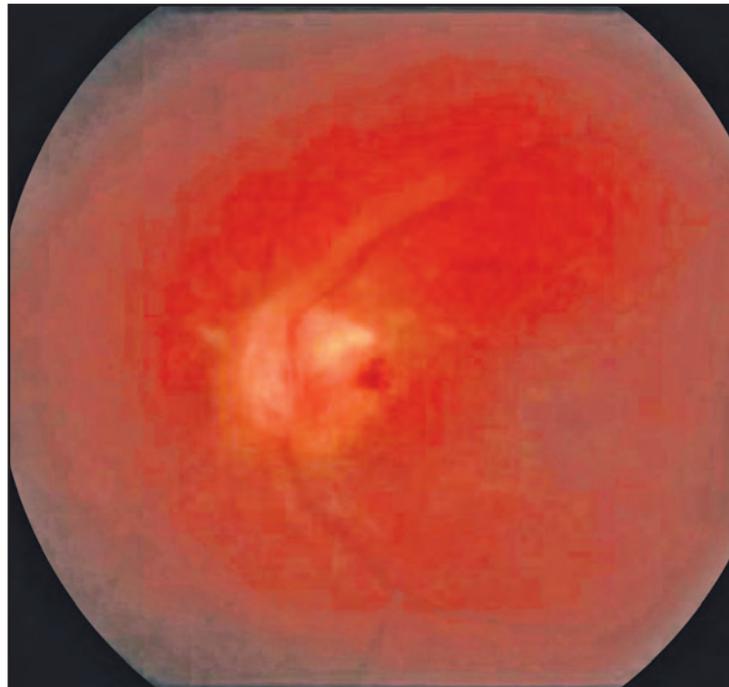


Figure 1. Moderate Vitreous Hemorrhage. Vitreous hemorrhages in reabsorption phase may cloud the vision centrally or appear as floaters that move around, affecting vision.



of the patient's most recent screening test is important (Figure 2). Such tests can include a routine urinalysis or serum glucose test. Comprehensive questioning regarding routine medications, other health conditions, family history and social circumstance is necessary in essentially all patients; in addition, specific clues regarding thalassemia or sickle cell disease or trait can be particularly helpful in patients with vitreous hemorrhage without an underlying likely etiology. A history of a malignancy or thyroid eye disease may uncover a history of radiation exposure. Multiple risk factors for cardiovascular dis-

ease will increase the likelihood of commonly encountered diagnoses of vascular occlusive disease.

Patients with vitreous hemorrhages who are asymptomatic (and therefore visit an eyecare provider much later than symptomatic patients) typically have underlying ocular pathology. Encountering patients with asymptomatic long-standing vitreous hemorrhages is unusual except for patients with poor acuity associated with a long history of an underlying risk factor for vitreous hemorrhage such as diabetic retinopathy (Figure 3).

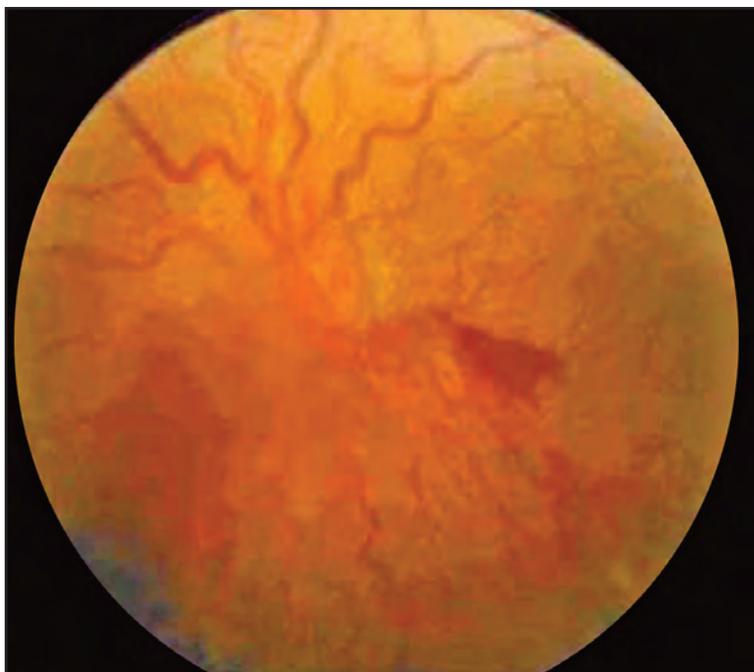


Figure 2. Vitreous Hemorrhage due to Proliferative Diabetic Retinopathy and NVD. Even if the patient ignores the possibility of having the disease, it is important to evaluate the pathology, especially if the anterior segment is normal or not related to the reduction in vision.

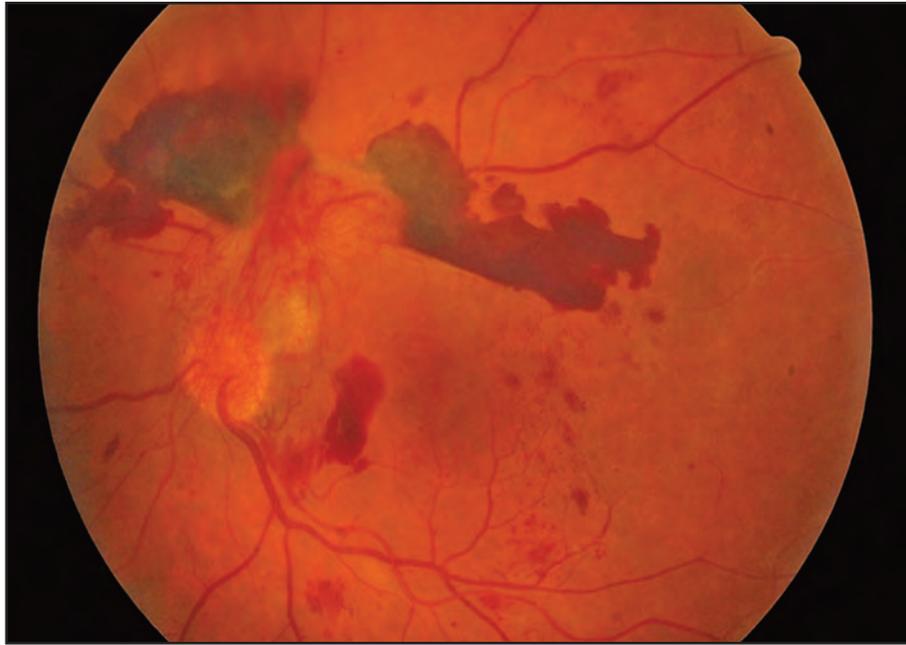


Figure 3. Proliferative Diabetic Retinopathy and NVD. A typical case were the macula still was not affected and the patient has not notice the severity of its retinal and visual problem.

Physical Examination

A direct or partial view of the underlying cause of a vitreous hemorrhage can in some circumstances be seen on physical examination. This view is usually available in less severe cases, when the patient may be asymptomatic. Examination alone may establish the diagnosis. Examination usually involves an indirect ophthalmoscope, which can be used with scleral indentation to obtain a kinetic examination of the peripheral fundus and observe clues regarding the presence of a peripheral break or tear if not observable

directly (Figure 4). Caution in this regard is necessary as the lamellar nature of the partially synergetic, gelatinous vitreous can commonly create, in a cleft of synergetic vitreous, the illusion of a break when none actually exists. Alternatively, the slit lamp (biomicroscope) may be used with various lenses capable of providing a highly magnified view of the retina to observe directly the culpable retinal or choroidal neovascularization, for example.

Commonly, however, on examination there is no view of the posterior segment other than that of the hemorrhage. The

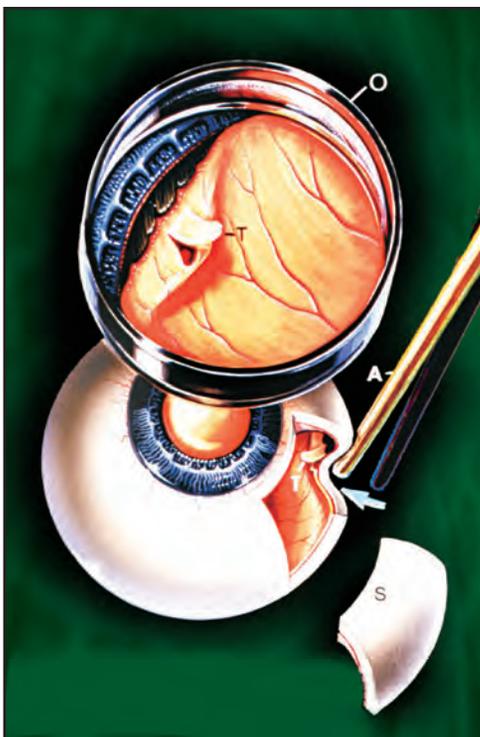
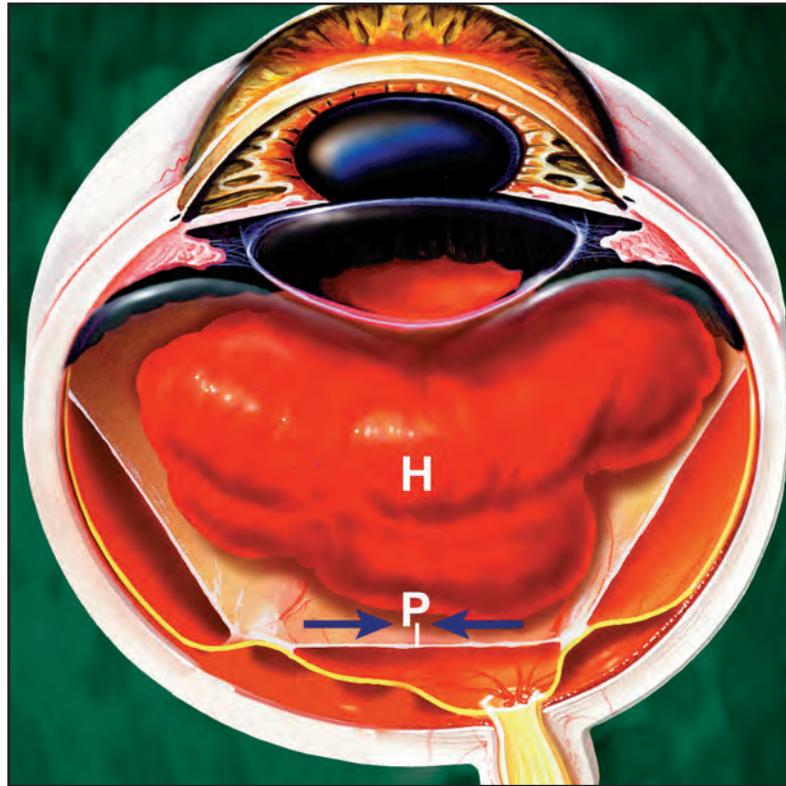


Figure 4: Method for Localizing and Marking Retinal Tears. This internal/external conceptual illustration shows how the site is marked on the external sclera that corresponds to the internal position of a retinal break. The indirect ophthalmoscope (O) is used for visualization while the sclera overlying the break is depressed (arrow-A). A section of sclera (S) is shown removed to reveal a cross section of the scleral depression made directly external to the retinal tear (T). The corresponding surgeon's view of this depression is seen through the indirect ophthalmoscope lens (O). (Art from Jaypee - Highlights Medical Publishers).

hemorrhage typically has a red appearance in the acute phase, and this red color may be preserved in long-standing hemorrhages as well (Figure 5). In long-term hemorrhages, the hemorrhage may appear white or gray after hemoglobin degradation. Often this phenomenon is noted in the inferior vitreous as gravity consolidates the hemorrhage. It may be more difficult to make the diagnosis of vitreous hemorrhage in patients with long-standing disease, and the differential diagnosis in these circumstances may expand to include posterior segment uveitides and neoplasia. Typically blood in the vitreous cavity is removed by macrophage digestion over time.

Patients may notice, and the ophthalmologist may observe on examination, that subtle abnormalities in the vitreous remain after the hemorrhage has cleared, but typically, the hemorrhages are entirely resorbed over time. The patient's age and the degree of vitreous syneresis influence the time needed for resorption. Other factors which affect the speed of resolution (also related to the extent of syneresis) are refractive error (i.e., vitreous volume), previous vitreous surgery or procedures, and the presence of comorbid inflammation. The etiology of the inflammation also must be considered as it may be secondary to the underlying etiology of

Figure 5. Recent Invasive Vitreous Haemorrhage (H). Initially the haemorrhage has a red appearance preserved for a considerable period of time. Months later it turns into a yellowish dark color usually difficult to reabsorb, and the formation of fibrous tissue (P). (Art from Jaypee - Highlights Medical Publishers).



the vitreous hemorrhage such as trauma or a uveitic process, especially one associated with peripheral retinal ischemia and secondary neovascularization.

It is essential that the fellow eye be examined when possible, since any findings there (or lack thereof) can significantly alter the likelihood of underlying etiologies in the differential diagnosis of the eye with the vitreous hemorrhage. The presence of diabetic retinopathy, retinopathy of sickle cell disease, or age-related macular degeneration may dramatically increase the probability of conditions in the fellow eye affecting the

eye with the vitreous hemorrhage. Such confounding factors may significantly alter the timing of intervention and frequency of repeat examinations for the eye with the vitreous hemorrhage.

Diagnostic Testing

B-scan ultrasonography is the test most commonly used to manage vitreous hemorrhages because this test may provide the underlying diagnosis and indicate whether a vitrectomy is needed and when. Ultrasonography is particularly critical for patients

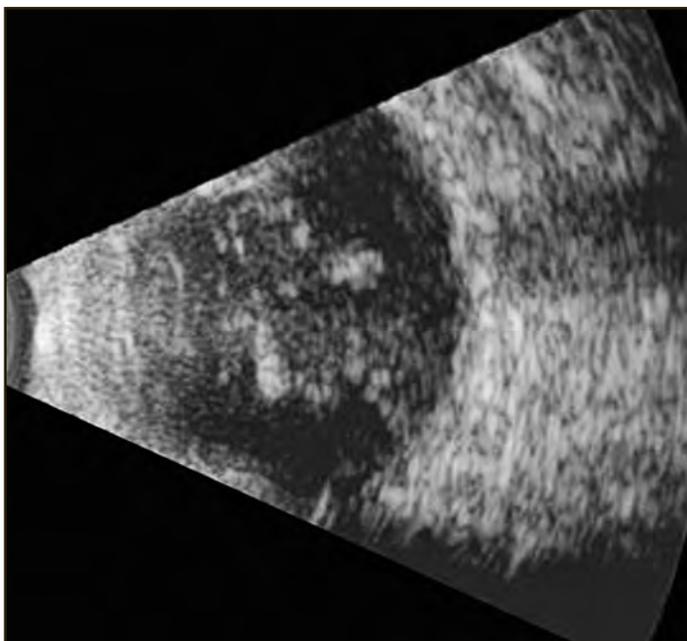


Figure 6. B-Scan of a Vitreous Haemorrhage. The vitreous is detached peripherally but adherent to the retina posteriorly probably due to proliferations. The hyper-reflectivity is due to vitreous hemorrhage, probably with some proliferations since it is still adherent to the retina. It is important to perform B mode ultrasonography to rule out retinal detachment or unsuspected choroidal tumors.

whose medical histories are unavailable or whose physical examination findings do not suggest a particular disease process and there is no view of the fundus (Figure 6). The foremost task of the ultrasonographer is to assess whether a retinal detachment or a retinal tear or break is present. Prompt vitrectomy is required for retinal tears or breaks and for retinal detachments that do not involve the macula. A hyperechogenic lesion in the macula suggests that the etiology may be exudative age-related macular degeneration,

or, less likely, a neoplastic process which may be encountered elsewhere as well.

For patients with risk factors for diabetes mellitus and no history of recent screening, a fasting serum glucose, glucose tolerance test, or glycosylated hemoglobin laboratory evaluation should be considered. For patients whose histories suggest a diagnosis of sickle cell disease or trait or thalassemia, hemoglobin electrophoresis may be considered.

Management

The management of vitreous hemorrhages can be straightforward when diagnostic ultrasonography clearly reveals a retinal detachment, tear or break. The management of a vitreous hemorrhage is typically conservative for diabetic patients. For patients with type II diabetes mellitus, observation every few months is indicated; for patients with type I diabetes mellitus, observation is generally indicated more often.¹ Generally after six months of a non-clearing vitreous hemorrhage in a type II diabetic, the benefits of surgical intervention (vitrectomy) outweigh the risks. The most significant factors in determining when a vitrectomy is indicated

for a non-clearing vitreous hemorrhage in a diabetic patient not previously examined are the type of diabetes mellitus (type I or II) and the age of the patient, since these factors relate directly to the presence or absence of a posterior vitreous detachment and the potential aggressiveness or rate of growth of the neovascularization (Figure 7). In young patients with type I diabetes mellitus, the posterior hyaloid is often attached and the rate of maturation of the neovascularization is generally rapid; the opposite is generally the case in older patients with type II diabetes. Bilateral vitreous hemorrhages with significant reduction in visual acuity are also an indication for more prompt intervention to obtain visual improvement.

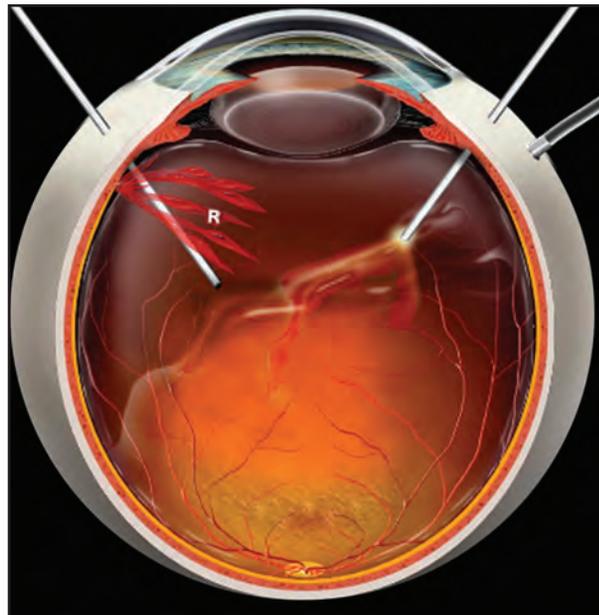


Figure 7. Vitrectomy for Vitreous Haemorrhage (R). Benefits of a vitrectomy should be discussed with the patient not only to clear the vision for diagnostic and visual purposes but to diminish the possibility of tractional factors affecting the retina. (Art from Jaypee - Highlights Medical Publishers).



Not since the advent of vitrectomy has the management of vitreous hemorrhage been altered more than with the widespread use of anti-VEGF (vascular endothelial growth factor) agents, which are particularly useful in diabetic patients or others with known risk factors for retinal (or choroidal) neovascularization. Before proceeding with vitrectomy, an intravitreal anti-VEGF agent is now commonly employed to regress neovascularization. While a non-clearing vitreous hemorrhage is a common indication for vitrectomy, the term “non-clearing” may be a misnomer, given the growing experience using anti-VEGF agents.² It appears that in many patients with vitreous hemorrhages that were previously considered to be non-clearing, the hemorrhages continue to occur subclinically. A significant number of these hemorrhages improve when the anti-VEGF agent is used, suggesting that the regression of neovascularization achieved with the anti-VEGF agent halts subclinical active hemorrhaging; the “non-clearing” vitreous hemorrhage is no longer clinically observed.

Oftentimes ultrasonography will not provide definitive diagnostic findings (e.g., no retinal detachment, tumor, or evidence of a tear or break), especially in the absence of a history of retinal pathology in the affected or contralateral eye. One exception may be the patient who has been evaluated routinely by an experienced eye-care practitioner who notes the presence of a posterior vitreous detachment, which may be identified as the etiology of the hemorrhage. There is a paucity of data to clearly guide the clinician in the management of patients with vitreous hemorrhages who have no history of or known risk factor

for diabetes mellitus or another predisposing condition. Clinicians have a highly variable approach in such circumstances, based on the clinician’s own experience and the patient’s particular situation. Depending on the patient’s general medical condition and the associated risks of surgical intervention, relatively prompt vitrectomy is considered by some vitreoretinal surgeons. Repeat evaluation is generally a matter of days among those clinicians who manage such patients conservatively. Even if empirical data were available, it may be difficult to apply the information to the specific clinical circumstance presented, as multiple factors (e.g., history of systemic vasculitis) can significantly increase or decrease the probability of a particular underlying pathology. Such factors can increase or decrease the risk-benefit ratio with regard to the timing of vitrectomy and the frequency of repeat examinations. For example, if patients develop symptoms of worsening acuity or photopsia, it may be less appropriate to defer vitrectomy.

Etiology of Vitreous Hemorrhage

Retinal neovascularization is a common etiology for vitreous hemorrhages. The most common causes of retinal neovascularization are proliferative diabetic retinopathy and venous occlusive disease. Other, less common conditions that may cause neovascularization include sickle cell disease, sickle cell trait, thalassemia, radiation retinopathy, and inflammation. In addition, central or branch retinal artery occlusion may give rise to ischemia and secondary retinal neovascularization (Figure 8).

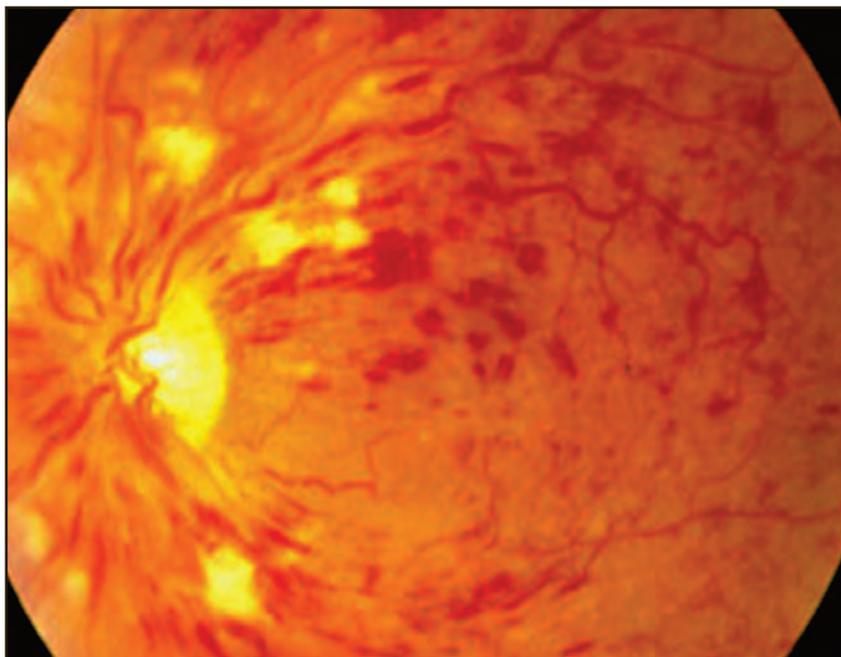


Figure 8. Retinal Vein Occlusion is One of the Common Etiologies of Vitreous Hemorrhages. Neovascularization can result from vascular retinal pathologies such as retinal vein occlusions, diabetic retinopathy, macular degeneration, sickle cell disease and trauma, etiologies that commonly affect vision in a suspect patient.

If a history of diabetes mellitus is reported by the patient, the history should be probed to determine the time since diagnosis, the degree of glycemic control and the presence of other microvascular complications of the disease. For the vast majority of patients with diabetes mellitus, neovascularization secondary to diabetic retinopathy will probably be the culprit, and therefore conservative management is usually most appropriate. An etiology of proliferative diabetic retinopathy should be viewed with some skepticism for patients with diabetes mellitus who have a history of a normal recent eye examination and are not pregnant or have had no recent

change in their glycemic control. For patients with known proliferative diabetic retinopathy, especially with a history of previous vitreous hemorrhage, the primary diagnosis of proliferative diabetic retinopathy for the current vitreous hemorrhage can be presumed the absence of contrary findings on examination and with B-scan ultrasonography. Additional testing for competing etiologies is probably not necessary unless unusual circumstances exist, such as a history of trauma or unusual findings on examination.

Almost universally, patients that present with a central retinal artery occlusion have



histories of such occlusions. It is possible, however, that some patients with poor pre-morbid (i.e., before the occlusion) vision, amblyopia, or other disease in a non-dominant eye may have a cilio-retinal artery supplying the fovea, which can lead to an asymptomatic central retinal artery occlusion. Patients with central retinal vein occlusion, branch retinal vein occlusion, or branch retinal arteriolar occlusions are often unaware of the underlying pathology until they become symptomatic with the vitreous hemorrhage, usually weeks after the neovascularization has begun to mature. On examination, it is often possible with indirect ophthalmoscopy and an adequate view of the retina to make the diagnosis of a retinal vein occlusion. After an arteriolar occlusion, in the convalescent period it is often difficult, if not impossible, to make a diagnosis of the occlusion as the retina often appears essentially normal on examination. After central retinal artery or branch retinal arteriolar occlusions, the minimal amount of retinal sequelae found with ophthalmoscopy warrant clinical contemplation regarding a diagnosis, but if neovascularization can be directly visualized then diagnosis is aided. Where an adequate view is possible, clues to the underlying etiology may be present, such as a thrombus, embolus, or arteriovenous crossing abnormality, although such clues are rare. Diagnosis is greatly aided by retinal angiography if an adequate view is possible.

Knowing the age of the patient may also be helpful for diagnosis. Etiologies such as retinal tears or breaks and posterior vitreous detachments usually present in the sixth and

seventh decades of life, which is also the most common time for retinal vascular occlusive disease to occur. Age is most helpful for diagnosing patients that are in their fourth and fifth decades of life, when typically patients do not have retinal vascular occlusions. In these patients, consideration of an etiology other than retinal occlusive disease is appropriate.

Evaluation for competing diagnoses such as hemoglobinopathies or radiation retinopathy with neovascularization is guided by the history. Hemoglobin electrophoresis can be useful, and anti-VEGF agents for sickle cell disease can be considered.³ Deciding when to perform a vitrectomy should be based on the risks and benefits for each individual patient; the procedure should be performed based on knowledge of the patient's pre-existing retinopathy and the duration and severity of the vitreous hemorrhage.

Other etiologies of retinal neovascularization that may result in vitreous hemorrhage can include any disorder that may result in retinal ischemia, such as retinopathies associated with the hemoglobinopathies and multiple heterogenic inflammatory disorders. Inflammation may cause ischemia indirectly,⁴ or may take the form of an autoimmune attack specifically against the retinal vasculature (i.e., phlebitis or arteritis).⁵

A vitreous hemorrhage without a pre-existing risk factor is most worrisome in terms of management. A careful history is essential in these patients. Occasionally a history of symptoms consistent with a



posterior vitreous detachment or retinal tear or break, such as photopsia, is obtained. If this is the case, then it may be likely that a retinal break or tear is present in addition to a posterior vitreous detachment. A careful inspection of the peripheral retina with the indirect ophthalmoscope is necessary in these patients; examination can be improved with scleral indentation. However, the hemorrhage often prevents or limits this examination, in which case obtaining B-scan ultrasonography is critical.

Choroidal neovascularization, most commonly from exudative age-related macular degeneration, may rarely result in a significant vitreous hemorrhage—occasionally massive enough to prohibit a view of the posterior pole. In such cases, examination of the contralateral eye can be more useful than ultrasonography in helping to support the diagnosis. It is important to conduct follow up with such patients, as choroidal melanoma in the macula may mimic this presentation. Choroidal neovascularization from other etiologies that allow egress of vessels through pathology in Bruch's membrane should also be considered, but are rare (e.g., myopic degeneration, angioid streaks⁶). Of those disorders in which large vitreous hemorrhage may result, the most common may be idiopathic peripheral choroidal neovascularization.⁷

The presence of intraocular neoplasia is seldom the etiology of vitreous hemorrhages,

but it can be the presenting symptom of an intraocular malignancy.

Conclusion

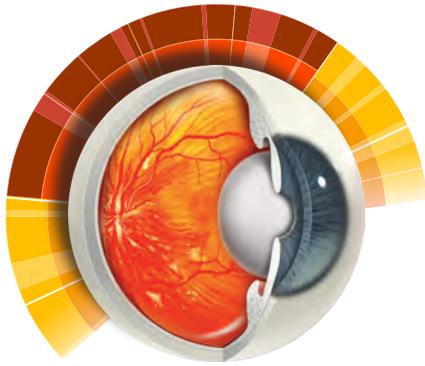
Vitreous hemorrhage is a common condition seen in the retina clinic. In many patients the underlying etiology and subsequent management is discernable from the history, physical examination and ancillary testing such as B-scan ultrasonography. However, for many other patients the etiology of the vitreous hemorrhage is not easily identified; for these patients, management can be appropriately recommended based upon the most likely and most consequential diagnoses in the differential. The timing of vitrectomy and the frequency of follow-up observation in patients with a vitreous hemorrhage varies among physicians and should be customized for each patient based on the probable diagnoses.

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Suprachoroidal Hemorrhage

MADHAVI KURLI, MD.,
RICHARD ROSEN, MD

Suprachoroidal hemorrhage is a rare but potentially devastating event that can occur spontaneously, or as a consequence of trauma or ocular surgery. It was first reported to have occurred during ophthalmic surgery by Baron de Wetzell in 1760.¹ Successful management of suprachoroidal hemorrhage was first described by Verhoeff in 1915.²

Anatomy and Pathophysiology

The suprachoroidal space is a potential space between the choroid and the sclera and normally contains about 10 μ l of fluid. When filled with blood it becomes a true space with boundaries at the scleral spur anteriorly and the optic disc posteriorly. The choroid is also attached to the sclera at the ampullae of the vortex veins, thus giving choroidal detachments their characteristic lobular appearance (Figures 1 and 2).

Many authors have described the mechanism leading to development of non-traumatic suprachoroidal hemorrhage.³⁻⁵ Hypotony appears to be the major precipitating event, leading to anterior displacement of the lens-iris diaphragm and in turn the retina and choroid. This can result in traction of a long or short posterior ciliary arteries, leading to rupture and hemorrhage.⁴ Hypotony can also cause serous choroidal effusion that can contribute to rupture of a long or a short posterior ciliary artery.⁶ In a rabbit model, four sequential stages in the development of suprachoroidal hemorrhage have been described.³

1. Engorgement of the choroidal capillaries.
2. Serous effusion into the suprachoroidal space.
3. Stretching and tearing of the blood vessels at the ciliary body base.
4. Massive hemorrhage from the torn vessels into the suprachoroidal space.



The long posterior ciliary arteries are especially prone to rupture during ciliochoroidal effusion due to their short connections between the scleral exit and outer choroid.⁷

Risk Factors

Risk factors for the development of suprachoroidal hemorrhage can be classified as ocular and systemic. Ocular risk factors include glaucoma, elevated intraocular pressure (IOP), increased axial length, aphakia, pseudophakia, inflammation and ocular surgery.⁸ Systemic risk factors include advanced age, atherosclerosis, diabetes mellitus, hypertension and blood dyscrasias.

Glaucoma, elevated IOP and increased axial length were found to be highly significant risk factors in the development of suprachoroidal hemorrhage by more than one author.⁸ These ocular conditions promote vascular necrosis and weaken the integrity of the long posterior ciliary arteries, making them more vulnerable to rupture. In axial myopia, loss of scleral rigidity and choroidal vascular fragility is presumed to be responsible for the development of suprachoroidal hemorrhage. In aphakia, more stretching and separation of the uvea from the sclera occurs during ciliochoroidal effusion due to loss of support from the lens and zonular apparatus.

Suprachoroidal hemorrhage can occur during ocular surgery or in the post-operative period. It has been reported with all types of intraocular procedures including cataract extraction, glaucoma filtration procedures, penetrating keratoplasty and vitrectomy. Older methods of cataract surgery and secondary

intraocular lens implantation procedures were associated with higher incidence of expulsive suprachoroidal hemorrhage, probably due to larger wounds and more prolonged hypotony. Phacoemulsification cataract extraction has reduced the incidence of suprachoroidal hemorrhage due to reduced manipulation and less pronounced fluctuations of intraoperative intraocular pressure. Glaucoma filtration procedures have a higher incidence of delayed suprachoroidal inflammation due to prolonged postoperative hypotony and inflammation. General anesthesia and intraoperative pulse rate greater than 90 beats per minute have also been implicated in the development of suprachoroidal hemorrhage.^{9,10}

Valsalva-type maneuvers (either from bucking during general anesthesia or vomiting in the post-operative period) result in an increase in the pressure gradient across the wall of a necrotic ciliary vessel, which can lead to rupture and subsequent suprachoroidal hemorrhage.¹¹

Preventive Measures

Preventive measures can be undertaken preoperatively and intraoperatively in patients at high risk for suprachoroidal hemorrhage. A thorough ocular and systemic evaluation should be performed preoperatively to look for evidence of hypertension, atherosclerosis, liver disease and blood dyscrasias. Diabetics should have their blood glucose under adequate control. Patients should also refrain from the use of aspirin and other non-steroidal anti-inflammatory agents in the immediate preoperative period.



Careful history taking and examination to identify glaucoma, aphakia, pseudophakia, severe myopia, recent intraocular surgery and suprachoroidal hemorrhage in the fellow eye are critical.^{12,13} Intraocular pressure needs to be adequately controlled before surgery. Softening the eye with carbonic anhydrase inhibitors or intravenous osmotic agents can be considered if necessary. Preoperative ocular compression, however, can lead to rupture of a weakened artery or may contribute to choroidal hyperemia and should be avoided.

Hypertension and tachycardia are significant risk factors for the development of suprachoroidal hemorrhage and need to be well controlled during the surgery. Preoperative phenylephrine should be used with caution due to its potential exacerbation of systemic hypertension. Since general anesthesia may increase the risk of suprachoroidal hemorrhage, its choice should be evaluated critically.

Post-operatively, Valsalva-like maneuvers must be carefully avoided. Stool softeners and careful instructions regarding limits to activity can be helpful. Inflammation should be controlled vigorously to avoid serous fluid accumulation in the suprachoroidal space and postoperative hypotony particularly in glaucoma filtration procedures should be avoided as they both pose significant risks for development of suprachoroidal hemorrhage.

Diagnosis and Management

Occurrence of suprachoroidal hemorrhage during surgery should be recognized im-

mediately and acted upon expeditiously to improve chances of a favorable outcome. Early signs include a sudden increase in intraocular pressure, firm globe, shallowing of the anterior chamber with forward displacement of the lens-iris diaphragm and loss of a red reflex. Immediate tamponade with closure of all surgical wounds or direct digital pressure should be performed, to avoid catastrophic expulsion of intraocular tissue. If intraocular contents are extruded, they need to be repositioned as soon as possible. Posterior sclerotomies may be performed to soften the eye and enable replacement of intraocular tissues. The long-term effects of posterior sclerotomies are somewhat controversial. Verhoeff recommended emergency posterior sclerotomies as treatment for suprachoroidal hemorrhage.² However, Lakhnpal showed in a rabbit experimental model that posterior sclerotomies can be detrimental in an acute setting with extension of the hemorrhage into the retina and vitreous cavity.⁶

Other intraoperative maneuvers include reformation of the anterior chamber to prevent vitreous entrapment into surgical wounds, removal of the lid speculum to reduce direct pressure on the eye, intravenous osmotic agents and lowering of blood pressure.

Postoperative suprachoroidal hemorrhage typically presents after uncomplicated glaucoma filtration procedures.¹⁵ The patient experiences sudden visual loss and severe ocular pain. Nausea, vomiting and headache may accompany it. On examination there may be shallowing of the anterior chamber with vitreous prolapse in aphakic or pseudophakic eyes, loss of red reflex and dark, dome-shaped



choroidal mounds (Figure 1). The immediate management includes lowering of the intraocular pressure, control of inflammation and pain management with cycloplegics and analgesics.¹⁶ Aspirin and nonsteroidal anti-inflammatory agents should be avoided.

In patients where media haziness prevents visualization of the suprachoroidal hemorrhage, ultrasonographic examination is extremely valuable. On B-scan examination, suprachoroidal hemorrhage presents as dome-shaped choroidal swellings which is partial or completely filled with fluid of

moderate internal reflectivity. These swelling may be so elevated in severe cases that they appear to kiss, threatening retinal apposition (Figure 2). A-scan tracings reveal a double-peaked, steeply rising spike that is characteristic of choroidal detachment, with low reflective spikes in the suprachoroidal space, suggesting hemorrhage.

Ultrasonography is an important means of determining the degree of hemorrhage in any choroidal detachment as well as a tool for gauging the progress and liquefaction of the clot, once the definitive diagnosis of

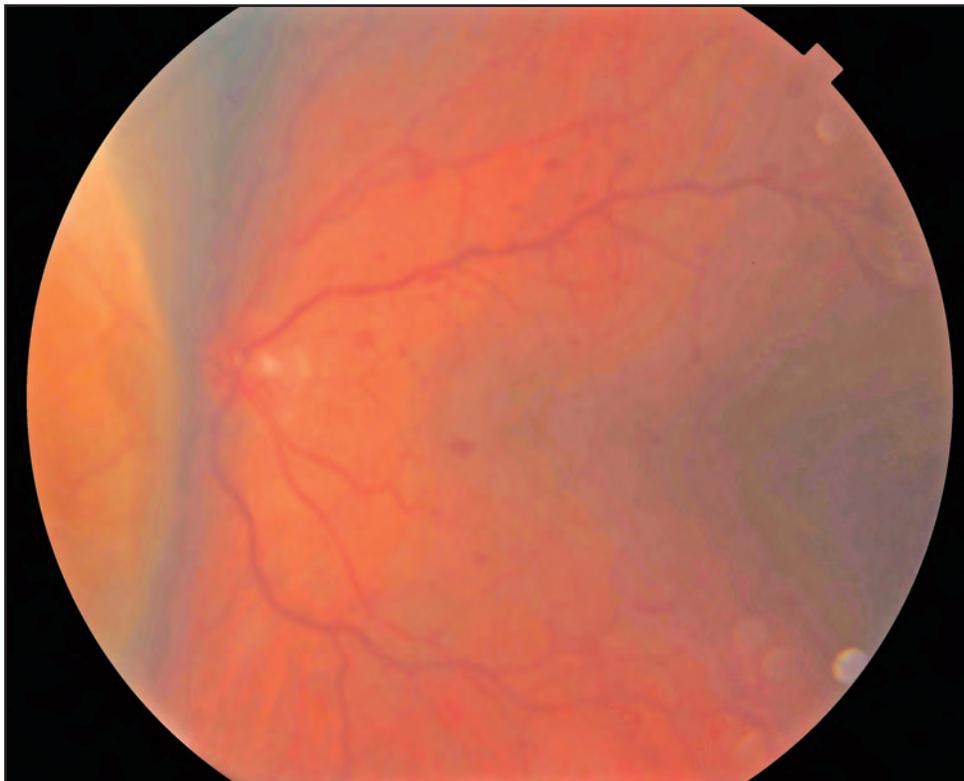


Figure 1: Color fundus photograph of the left eye showing a suprachoroidal hemorrhage nasal to the disc.

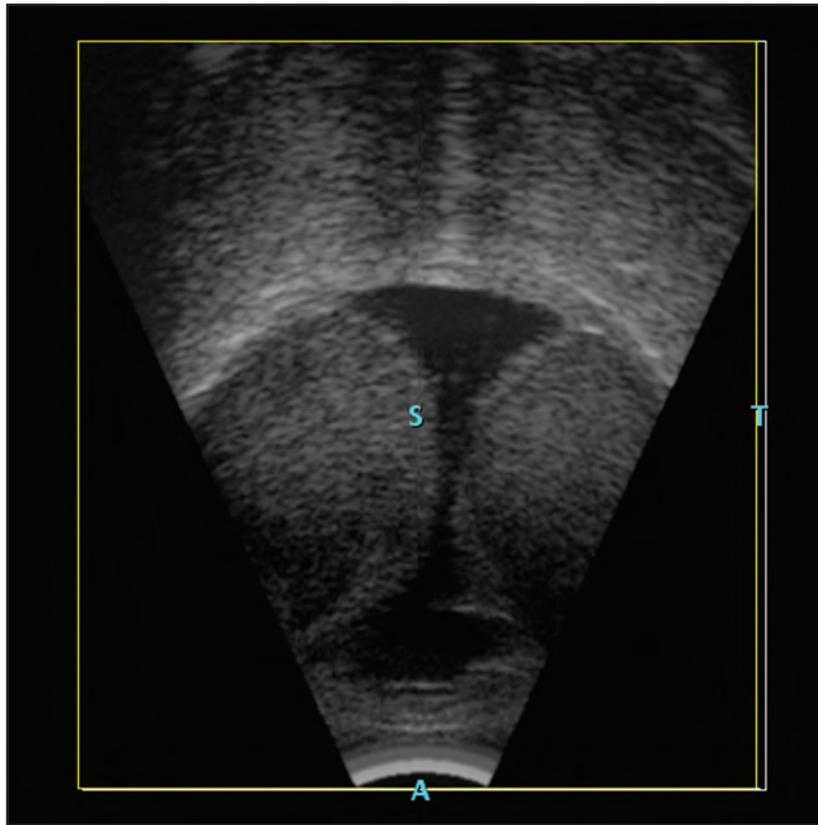


Figure 2: Ultrasonography demonstrates dome-shaped suprachoroidal hemorrhages.

suprachoroidal hemorrhage has been made. Fresh clots appear ultrasonographically as highly reflective masses with irregular shape and structure. As the clots liquefy, they become less reflective. Liquefaction time of these hemorrhages has been reported at between 7 to 14 days.¹⁷ Decisions regarding timing of surgical intervention are often aided by ultrasound findings, but should not be dictated by them. While complete liquefaction of the clotted hemorrhage can facilitate attempts at evacuation and reduce complications by mini-

mizing the need for probing and excessive manipulation other factors such as degree of pain, extent of vision loss, condition of the eye, and other patient factors need to be considered as well. Early intervention in attempt to remove even part of the hemorrhage in the hope of maximizing the chances for visual recovery may be a reasonable consideration in monocular patients; realizing that an additional procedure may be needed several days later.



Secondary Surgical Management

Before the decision to operate is made, it is important to determine whether expulsive or delayed suprachoroidal hemorrhage has occurred, as the long-term prognosis for each differs. Some authors have proposed early surgical drainage. Major indications for earlier intervention include central retinal apposition, retinal detachment, breakthrough vitreous hemorrhage, vitreous incarceration in surgical wounds, increased IOP and intractable pain.¹⁸ Rhegmatogenous retinal detachments are the major indication for surgical intervention. Serous retinal detachments can be observed closely for evidence of progression since they typically resolve spontaneously. Central retinal apposition is a relative indication for earlier surgical drainage. Some authors have recommended longterm intraocular tamponade with gas or silicone oil.¹⁸ Poorer visual outcome is associated with increased complexity of the suprachoroidal hemorrhage. Retinal incarceration in the wound is especially associated with a poor prognosis.¹⁹

Surgical intervention can involve one of two options:

1. External drainage of the suprachoroidal hemorrhage.
2. External drainage procedure combined with a vitreoretinal surgery to remove vitreous hemorrhage or retained lens material, to relieve vitreoretinal traction or to reestablish normal posterior segment anatomy.

Optimal timing of the drainage intervention is critical for a favorable outcome. Mean clot lysis time is 7 to 14 days. Draining a suprachoroidal hemorrhage that is still mostly clotted is usually unsuccessful and can lead to further damage. It is therefore generally recommended that drainage procedures be carried out 1 to 2 weeks after the development of suprachoroidal hemorrhage, however, earlier attempts may be considered in particular cases. Clot lysis is best confirmed by ultrasonography.

Drainage sclerotomies are created equatorially in the quadrants of the hemorrhage. It is important to peel back the conjunctiva wherever possible, identify and tag the rectus muscles with sutures. This enables placement of the sclerotomies sufficiently posteriorly to facilitate adequate drainage. The IOP should be supported using an anterior chamber maintainer during the procedure. This enables the drainage of lysed blood through the sclerotomy without allowing the eye to become soft (Figure 3). A cyclodialysis spatula can be used to assist in draining the hemorrhage, but care must be exercised to probe along the inner surface of the sclera in order to avoid damaging the overlying retina in areas of shallow elevation. Continuous air-infusion can also be useful to maintain the IOP during the procedure, especially in aphakic eyes. A careful inspection for evidence of vitreous incarceration or vitreoretinal traction should also be undertaken at the time of the procedure.

If vitreoretinal surgery is planned with the drainage procedure, the sequence of maneuvers is crucial to prevent complications.

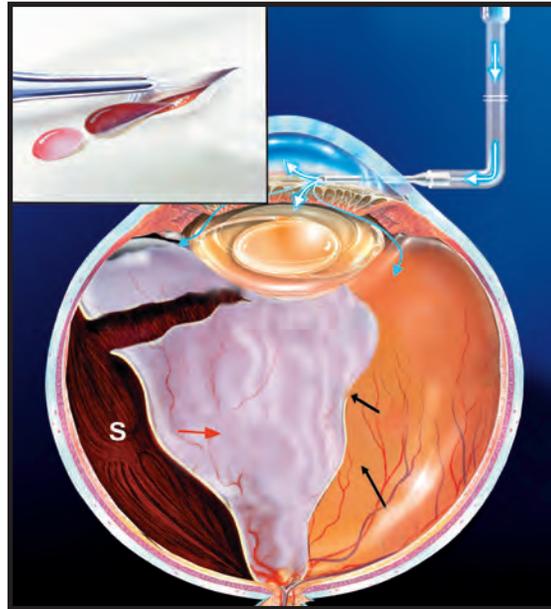


Figure 3. Suprachoroidal Hemorrhage Surgical Management. Once ready for surgical management, the anterior chamber should be placed to maintain a stable IOP (blue arrows) during lysed blood drainage (black arrows). Before the decision to operate and remove the suprachoroidal hemorrhage (S) is made, it is important whenever possible to determine the condition of the retina and posterior segment (retinal detachment-red arrow, vitreous hemorrhage, etc). The drainage sclerotomy should be performed sufficiently posteriorly to facilitate adequate maneuvers and drainage (inset). (Art from Jaypee - Highlights Medical Publishers).

It is imperative to begin drainage of the hemorrhage first as the anatomy is usually distorted in these eyes which could lead to misplacement of a posterior infusion cannula into the suprachoroidal space instead of the vitreous cavity. A 6 mm infusion cannula is particularly helpful to avoid such a complication. Perfluorocarbon liquid can be used to internally assist pushing posteriorly trapped blood from beneath the macula toward the more anteriorly located exit sclerotomies. After the bulk of the choroidal hemorrhage has been drained and a more normal anterior anatomy has been established, the three-port

vitrectomy can be performed. Retinal detachments can then be addressed. Long-term internal tamponade with intraocular gas or silicone oil is often required.

Prognosis

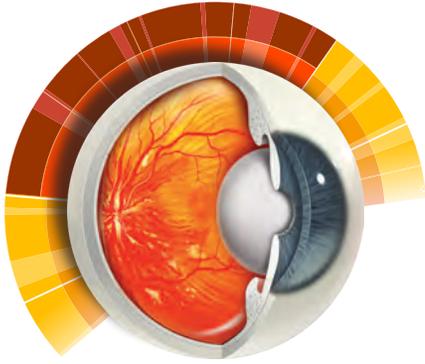
Expulsive choroidal hemorrhages generally have a poor visual prognosis and secondary surgical intervention may not be helpful for all patients. Second procedures should be based on clear indications for intervention. In delayed suprachoroidal hemorrhage, secondary drainage should



generally be planned when clot lysis is nearly complete and may be combined with vitreoretinal procedures to obtain the most favorable outcome. Prognosis appears to depend upon the extent of ischemia, which may relate to whether the vessel which initiates the hemorrhagic event is arterial or venous, the degree of anatomic disorganization which resulted from the event, and the extent of toxicity produced by the blood on the overlying photoreceptors. Careful but decisive intervention can offer an opportunity for some visual recovery in even the most severe cases.

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Management of Traumatic Subretinal and/or Suprachoroidal Hemorrhage

GERARDO GARCÍA-AGUIRRE, MD.,
VIRGILIO MORALES-CANTÓN, MD.,
HUGO QUIROZ-MERCADO, MD

Introduction

Non penetrating trauma is the most common of ocular injuries⁽¹⁾. Although in most cases there is no treatment that can avoid posterior pole damage, early diagnosis and prompt treatment may prevent severe visual loss.

Non perforating trauma of the globe can result in a great variety of alterations in the posterior pole. These can include: preretinal, intraretinal and subretinal hemorrhages, suprachoroidal hemorrhage, Berlin's edema, cystoid macular edema with subsequent formation of a macular hole, retinal pigment epithelium (RPE) hematomas and choroidal ruptures⁽²⁾. Structural modifications can spare visual function or can cause up to total vision loss. Probably, Berlin's edema represents

the more frequent alteration detected in non penetrating ocular trauma. Nevertheless, hemorrhages are not infrequent and most of them are associated with choroidal rupture⁽³⁾. Since subretinal and suprachoroidal hemorrhage are two different clinical entities, they will be dealt with separately in this chapter.

TRAUMATIC SUBRETINAL HEMORRHAGE

There are many causes of the accumulation of blood in the subretinal space. Bleeding can come from either retinal or choroidal vessels. Examples of bleeding from retinal vessels include rupture of an arterial macroaneurism with bleeding under the neurosensory retinal space, or a Valsalva hemorrhagic retinopathy^(4,5,6). Subretinal hemorrhages, however,



usually come from the choroidal vessels. As examples, we can mention the subretinal neovascularization associated to age-related macular degeneration (ARMD), or to the Presumed Ocular Histoplasmosis Syndrome, and the choroidal ruptures of myopia. Likewise, complications in retinal surgery can cause choroidal bleeding when subretinal fluid drainage is made. Blunt ocular trauma as well as penetrating, can also cause choroidal bleeding, with accumulation of blood in the subretinal space.

Blood in this space results in photoreceptor damage that can compromise visual function permanently. In humans it can cause a permanent decrease in visual acuity. Bennett et al⁽⁷⁾ analyzed various etiologies related to macular subretinal hemorrhage retrospectively. He showed that the etiology plays an important role in final visual acuity. Those patients with ARMD had an average final visual acuity of 20/1700, while visual acuity after hemorrhages secondary to traumatic choroidal ruptures averaged 20/35.

Because of these findings, recent interest has arisen to develop surgical techniques that allow the evacuation of massive subretinal hemorrhages, to avoid possible visual acuity impairment and sometimes achieve improvement. In this chapter we focus on the mechanisms that cause choroidal and retina damage secondary to trauma and the presence of blood in the subretinal space and the surgical possibilities to achieve its evacuation.

Origin of Subretinal Blood in Trauma

Blunt, non penetrating trauma of the eye can present multiple manifestations in the posterior segment. Almaca et al⁽⁸⁾ reviewed the records of 445 patients and found that that 9.4% presented with Berlin's edema, 8.1% showed choroidal ruptures, and 3.6% had macular hemorrhages.

Hemorrhages in the posterior pole can be observed clinically in different levels. Most are intraretinal, being round and small when located in the external layers of the retina or in a flame-shaped form when found in the nerve fiber layer. These hemorrhages can also be preretinal.

Severe blunt trauma can also cause sub pigment epithelial, subretinal, intrachoroidal, and suprachoroidal (between the choroid and sclera) hemorrhages (Figure 1). In 1968, Gitter et al⁽⁹⁾ reported the case of a patient with blunt trauma to the eye, who presented with a localized hemorrhage under the retinal pigment epithelium. The hemorrhage was caused by a choroidal rupture, detected after blood reabsorption.

In order to understand the origin of post-traumatic hemorrhages it is necessary to analyze the possible causes of these injuries in different pathologies. In cases of subretinal hemorrhage associated with choroidal neovascularization secondary to ARMD, it has



Figure 1: Fundus photograph showing subretinal hemorrhage after blunt trauma to the eye.

been reported that blood can come from arterial vessels located in disciform scars. These vessels can have continuity with choroidal arteries. El Baba et al⁽¹⁰⁾ speculated that blood or serum can leak from neovascular tissue and produce an RPE detachment. This could produce pressure over the entering artery and the vein coming from the fibrovascular scar causing necrosis and rupture of vessel walls, allowing the passage of blood to the subretinal space.

In general, it is considered that subretinal blood located in the macula secondary to trauma comes from vessels of the choriocapillaris and choroid. The bleeding mechanism can be due to rupture of vessels, with or without choroidal rupture. Gass⁽¹¹⁾ has demonstrated that a great variety of pathologies associated

with Bruch's membrane disruption in the macular area can set the scenery of choriocapillaris or choroidal neovascular bleeding, producing hemorrhagic detachments. In these cases the firm adherence of the RPE at the margins of the hemorrhage acts as a barrier confining the detachment and giving it a dome-like shape.

Histopathology of Choroidal Damage

Damage provoked by blunt trauma to the globe can affect the choroid and the RPE. Damage to the choroid manifests usually as choroidal ruptures, while damage to the RPE manifests as contusion (Figure 2).

In RPE contusion, cellular edema can provoke a serous retinal detachment. In a case reported by Friberg⁽¹²⁾, a creamy color of the RPE was reported 48 hours after trauma. Angiography showed progressive staining of the RPE. Although the pigment epithelium appeared opaque, there was no hypofluorescence. After five months, transmission defects were detected but there was no staining of the RPE.

According to the study by Blight et al,⁽¹³⁾ there is intracellular edema of the RPE due to rupture of the internal membranes. This damage also provokes defects in the external segments of the photoreceptors. The cellular edema can show resolution at three weeks and the zonula occludens appears intact in



this period. These results suggest that contusion can cause damage to some membranes of the RPE cells, sparing their structure in another cellular layer.

Choroidal ruptures can be divided into direct or indirect.⁽¹⁴⁾ Direct ones occur anterior to the site of impact and generally are parallel to the ora serrata. Indirect ones are posterior, far from the site of impact and generally shaped like a crescent, concentric to the optic nerve (Figure 2). Usually they represent a rupture in Bruch's membrane and choriocapillaris although a complete transection of choroid can exist.

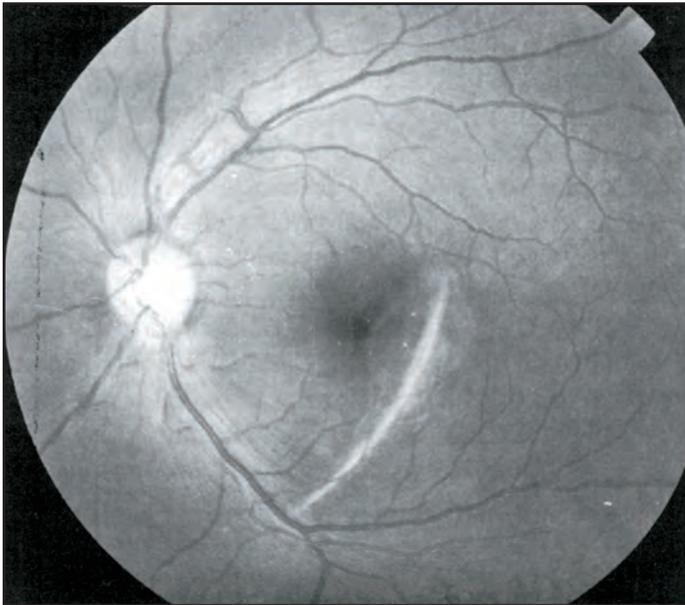


Figure 2: Fundus photograph of a crescent-shaped choroidal rupture, concentric with the optic disc. Note an associated RPE contusion in the superior portion of the rupture.

The mechanism of choroidal rupture in trauma can be explained by means of the contrecoup forces a "pressure wave" originated in anterior segment and meeting at the posterior pole. Bruch's membrane ruptures due to its relative inelasticity compared to the retina and sclera.⁽¹⁵⁾ The most complete description of the histopathology of choroidal ruptures is the one from Aguilar and Green⁽¹⁶⁾ in which histopathological findings of 47 eyes were reported. In this study, the time between trauma and the histopathological study varied between hours and 25 years. The presence of hemorrhages in the acute period was common and an important association between them and choroidal rupture was observed. These hemorrhages were related to a fibroblastic proliferation observed between 4 and 14 days after trauma. Hyperplasia of the RPE is a common finding in these cases, and mature scars can be observed 3 or 4 weeks after trauma.

These scars form with neovascularization; in most of the cases the new vessels regress with no sequelae. Nevertheless, some cases can present extension of the vessels to the vitreous cavity. In this series, only one case showed the presence of blood vessels located in the sub-RPE space. These vessels had the common characteristic of being essentially acellular. Accordingly it is possible to suppose that blood located in the subretinal space in the traumatic cases can come from a choroidal rupture. However, some cases do not show this defect once the hemorrhage clears.



As in other pathologies, it is probable that the passage of new vessels from the choriocapillaris into the subretinal space is permitted by the ruptures found in Bruch's membrane associated with choroidal ruptures. Nevertheless, a biochemical theory has been postulated, with the stimulation for neovascularization originating in the RPE or in the neurosensory retina.^(17,18)

There are mainly three causes that can provoke diminution of visual acuity in

choroidal ruptures: extension of the rupture that involves the fovea (Figure 3), presence of choroidal neovascularization, and blood accumulation in the subretinal space and sub-RPE (Figure 4). Associated choroidal neovascularization can appear months or years later following trauma⁽¹⁹⁾ and could be associated with serous or hemorrhagic retinal detachment. Successful argon laser treatment of this neovascularization has been reported.

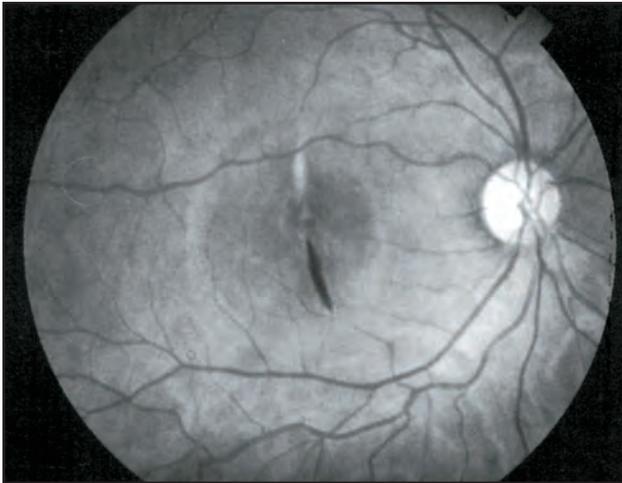


Figure 3: Crescent-shaped choroidal rupture, which passes under the fovea.



Figure 4: Choroidal rupture with a secondary intraretinal and subretinal hemorrhage.



Visual acuity loss secondary to choroidal ruptures can also be explained by a post-traumatic pigmentary retinopathy.

In 1980 Hart⁽²⁰⁾ reported campimetric findings associated with choroidal ruptures. He observed central scotomas that gradually showed improvement of sensitivity after weeks or months following the trauma. Nevertheless some cases presented field defects apparently located in areas far from the choroidal rupture and presumptively due to post-traumatic pigmentary retinopathy. Similar data were found in a study that we made using the Rodenstock Scanning Laser Ophthalmoscope.⁽²¹⁾ We detected the presence of absolute scotomas at the site of the choroidal rupture in 80% of cases. The extension of the scotomas was larger than the choroidal defects in 30% of cases. These findings could explain why some patients who do not show compromise of the fovea by choroidal rupture can present a visual acuity impairment.

Toxicity of Subretinal Blood

It has been documented that blood localized in the subretinal space is toxic and provokes irreversible damage to photoreceptors after 24 hours. In studies made in rabbits, Glatt and Machemer⁽²²⁾ demonstrated that blood produces damage to photoreceptors and the internal nuclear layer 24 hours after experimentally injecting blood into the subretinal space. They felt that the probable causes of these alterations were due to a combination of mechanical damage to the external segment of the photoreceptors caused by clot contraction, toxicity by iron components, and the barrier of the clot.

Blood clots in this space form a mechanical barrier between the retina and the RPE. This produces a limitation in the metabolic exchange that is essential for the appropriate functioning of these structures. This kind of barrier also has been demonstrated in rabbits following silicone injection.⁽²³⁾

Green and Key⁽²⁴⁾ demonstrated histopathologically in humans that there is loss of photoreceptors and thinning of external nuclear layer in cases with serohemorrhagic detachment of retina.

Some reports of subretinal hemorrhages describe a poor visual prognosis. In 1986 El Baba⁽¹⁰⁾ reported 15 patients who presented subretinal or vitreous hemorrhage secondary to ARMD. Ten of these showed extensive subretinal hemorrhage. At the beginning, visual acuities were 20/400 or worse and subsequently in the follow up, it was determined that final visual acuity remained in hand movements or worse. Histopathological results showed likewise cellular damage of photoreceptors with diffuse cellular loss (Figure 5).

In 1991, Toth et al.,⁽²⁵⁾ reported similar changes in the retina of cats when experimentally injecting blood subretinally. Twenty-five minutes following the injection, interdigitated fibrin was observed in the photoreceptors. At one hour, fibrin layers were causing a total detachment of the external and internal segments of the photoreceptors. Fourteen days later, an extensive and severe destruction of external layers of the retina was observed. According to these histopathological findings, fibrin may be the causative agent of major

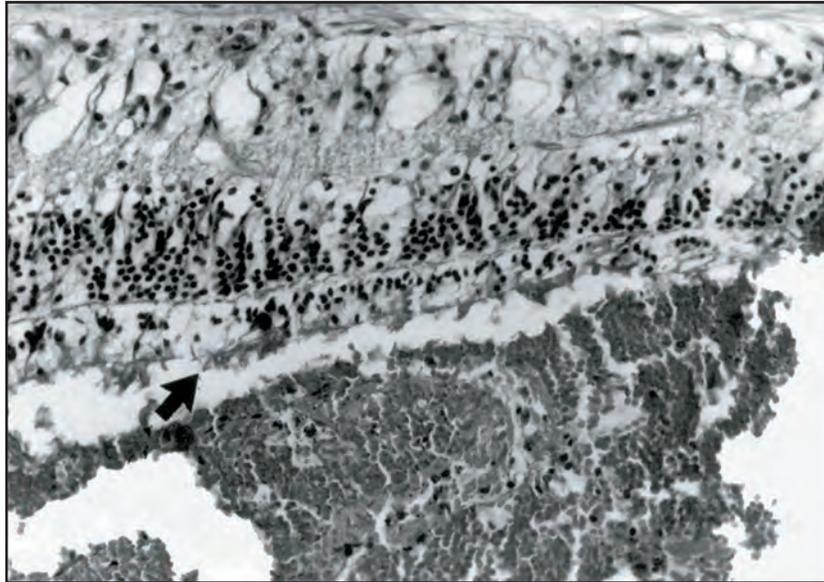


Figure 5: Histopathologic section of the human retina with a subretinal hemorrhage demonstrating severe damage to photoreceptors (arrow). (Courtesy of Drs. A. Gomez-Leal and A. Rodriguez-Reyes, Mexico City, Mexico).

damage to photoreceptors by producing traction with subsequent rupture and separation.

The cleansing of blood from the subretinal space includes phagocytosis and fibrinolysis. Macrophages are present that phagocytize the hemorrhage and degenerate when migrating to the RPE. Müller cells and the RPE itself also phagocytize cellular detritus and transform hemosiderin to ferritin. This process can function well in small hemorrhages, but, when the hemorrhage is extensive, iron radicals are released due to a saturation of iron binding proteins. The free iron poisons the enzymatic intracellular functions. Koshibu⁽²⁶⁾, using albino and pigmented rats,

demonstrated macrophages surrounding the erythrocytes, after subretinal injection of autologous blood through the choroid. Some erythrocytes were surrounded by RPE cells that showed degenerative changes probably due to the toxic effect of the iron released by the process. Some of the ferritin particles in the RPE had migrated through Bruch's membrane into the endothelial cells of the choriocapillaris.

Neurosensory retina showed extensive degenerative changes after 3 months. This cellular degeneration was similar to that found in cases of hemosiderosis bulbi and probably was due to the effect of free toxic iron and the metabolic alteration following



degeneration of the RPE, Müller cells and endothelial cells of the retinal capillaries.⁽²⁷⁾

Therapeutic Possibilities

The management of subretinal hemorrhage depends mainly on what caused it, its location, and its extent. The choices include observation with no intervention, vitrectomy with mechanical extraction of the clot, and vitrectomy using fibrinolytic agents in order to achieve lysis of the clot. In general, we

can mention that every one of them has risks and advantages. That is why it is very important to judge the risk/benefit in order to decide on a surgical procedure.

In many cases, the hemorrhage is not extensive and is not thick, with a minimal elevation of the retina in the macular area (Figure 6). In these cases it may be convenient to observe the case because it is possible that a surgical procedure does not offer benefits and can be associated with intra and post-operative complications.

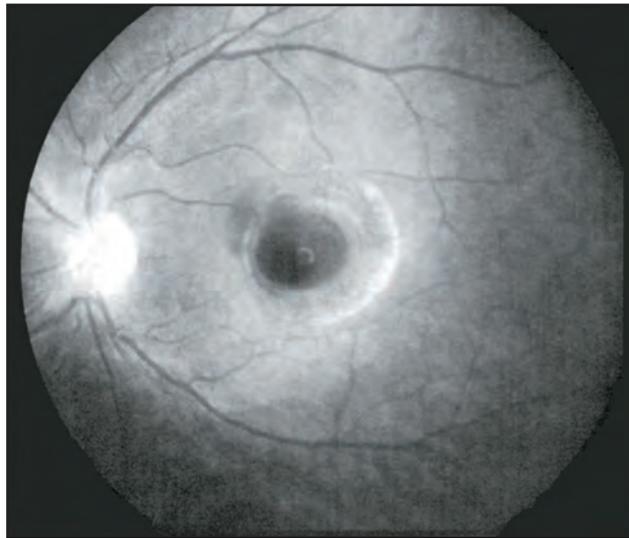


Figure 6: Patient with a small macular subretinal hemorrhage secondary to trauma with minimal elevation of the retina. Visual acuity 4/200.



It is very important to determine what cases can be candidates for a surgical procedure of this kind, because there are cases that can have a satisfactory evolution with conservative treatment. In 1990, Bennett et al.⁽⁷⁾ analyzed the factors that can participate in visual prognosis of subretinal hemorrhages secondary to different etiologies. Twenty nine cases were reviewed of which 7 presented hemorrhage secondary to trauma. After assessing the cause of the hemorrhage, the size, and thickness of it, it was determined that the hemorrhage diameter does not have a significant prognostic value. The hemorrhages of greater thickness showed a final visual acuity worse than those less thick. On the other hand, the ones secondary to ARMD had worse final visual acuity than the ones caused by other pathologies like choroidal ruptures. The most important predictive factor was the presence of ARMD more than the hemorrhage thickness itself ($p=.03$).

Hemorrhages secondary to trauma may compromise vision less as long as there is no underlying base pathology such as ARMD with atrophic areas of the RPE and choriocapillaris, with subretinal hemorrhages⁽²⁸⁾, and subretinal neovascularization. Nevertheless a choroidal rupture can directly affect visual acuity without foveal compromise.

Berrocal et al⁽²⁹⁾ retrospectively assessed cases of macular subretinal hemorrhage secondary to different pathologies. Of 31 patients studied, 20 presented hemorrhage secondary to ARMD, 2 from trauma, and the 9 remaining eyes secondary to other pathologies. Of the eyes that presented with ARMD, eight

(40%) of the 20 showed improvement of visual acuity (> 2 Snellen lines), six (30%) had a final visual acuity of 20/80 or better and three (15%) had visual acuity of 20/40 or better. In the group of patients not related to macular degeneration, five (45%) of the 11 showed vision improvement and five (45%) achieved a visual acuity of 20/40 or better. The average follow up time in the study was 29 months. Even though the number of patients was limited in this study, Berrocal et al. conclude that in general, patients that do not have associated subretinal neovascular membranes may have a better visual prognosis.

The base diagnosis in these cases is important in order to weigh the visual prognosis when surgical evacuation of subretinal blood is considered. Wade et al⁽³⁰⁾ and Vander et al⁽³¹⁾, demonstrated that in cases treated by means of subretinal blood removal in patients with ARMD, there was not a good recovery of visual acuity.

In patients operated in the group of Vander, surgery was made on the first week of appearance of the hemorrhage associated symptoms. Visual acuity improved in 36% of the cases. These authors postulated that the low visual acuity recovery could be due to two factors: the probable damage in photoreceptors when extracting the blood clot with no fibrinolytic agents, and the degenerative changes of the base illness.

In attempting to improve the visual possibilities of patients with macular hemorrhage, some investigators have developed



new surgical techniques in order to evacuate subretinal hemorrhage associated with various pathologies.

In 1983, Dellaporta reported a case of massive subretinal hemorrhage in which he passed an endodiathermy needle through retina, choroid and sclera achieving the passage of blood to the vitreous cavity.⁽³²⁾ Final visual acuity improved from 3/200 to 20/25. Hanscom and Diddie⁽³³⁾ used modern techniques of vitrectomy making internal retinotomy, endodrainage and fluid-air exchange in order to evacuate the subretinal blood. Later, de Juan and Machemer⁽³⁴⁾ used vitrectomy techniques in 4 eyes with a diagnosis of macular subretinal hemorrhage. Three of the operated eyes, showed also subretinal scars that were removed at the same time. In this procedure, it was either necessary to use multiple fluid-air exchanges in order to achieve the evacuation and expression of the blood clot or to make extensive retinotomies in order to accomplish this. The visual acuity improved in 3 of the 4 eyes. Nevertheless, 2 eyes presented postoperative complications characterized by retinal detachment and associated proliferative vitreoretinopathy (PVR). This work showed that it was possible to evacuate blood from the subretinal space by means of vitrectomy and retinotomy.

In 1990, Wade et al⁽³⁰⁾ reported the surgical results of 14 patients with a diagnosis of macular hemorrhage. They divided patients in groups depending on the etiology of the hemorrhage. Nine were secondary to retinal detachment or complications of surgery and 5 to ARMD.

The blood removal was made by means of a single or multiple retinotomies and the blood was aspirated with an extrusion cannula. In some cases forceps were used in order to extract the clot. The preoperative visual acuities not associated to ARMD were from 1/200 or worse in 8 of the 9 patients and 2/200 or worse in the cases associated with macular degeneration. After surgery, 8 of the 9 eyes not related to macular degeneration showed an improvement of vision of 20/400 or better while in 3 of the 5 patients of the group with macular degeneration they showed slight improvement of the visual acuity, but none better than 5/200. Postoperative complications reported in the study included subretinal recurring bleeding in three eyes and subretinal massive fibrosis in two eyes. The authors concluded in their work that the bad visual acuity obtained in the group of patients with macular degeneration was due to the presence of pre-existent macular disciform degenerative process.

When surgery is considered, the evolution time of the hemorrhage must be taken into consideration. Rubsamen et al⁽³⁵⁾ have described the usage of immediate pars plana vitrectomy for the drainage of massive subretinal blood due to complications of surgery for retinal detachment. In the reported cases, no fibrinolytic agents were used and in all of them, expandable gases were used at the end of surgery in order to achieve a tamponade of the lesions. In 7 of 9 eyes, final visual acuity was 20/80 or better. The authors reported little extension of the retinotomies due to the fresh clot at the moment of surgery and that the retina was mobile. The results of



the visual acuities in this report as well as in others, demonstrate that cases with AMD treated with surgery show worse results.

Dellaporta in 1994⁽³⁶⁾ made intense applications of argon laser over the retina that covered the dark blood in the subretinal space. The resulting hole allowed blood to pass to the vitreous cavity. After a month, visual acuity improved to 20/60.

Usefulness of Recombinant Tissue Plasminogen Activator

Fibrin plays an important role in the retinal damage caused by subretinal hemorrhage. That is why several investigators have used fibrinolytic agents such as the recombinant tissue plasminogen activator (tPA) initially in animals and later in humans showing its usefulness in clot lysis. Lewis et al⁽³⁷⁾ proved the efficacy and safety of tPA in rabbit eyes when injected in the subretinal space in induced hemorrhages. There was a rapid clot clearance in eyes in which tPA was administered compared with the ones with saline. There were no toxic effects reported when using 25 $\mu\text{g}/0.1$ ml and 50 $\mu\text{g}/0.1$ ml concentrations.

The beneficial effect in the usage of tPA in subretinal injections can be explained by three factors: 1) lysis of fibrin located between the photoreceptors, 2) dilution of the toxic factors released by the lysed erythrocytes; and 3) reduction of the barrier effect caused by the blood clot limiting the

metabolism between photoreceptors and the RPE. The fibrin lysis between photoreceptors probably is the most important factor in the damage prevention because the balanced saline solution injection can also dilute toxic factors and reduce the barrier effect.⁽³⁸⁾

The usefulness of tPA in the subretinal clot has been documented by other authors.^(39,40,41) Coll et al⁽⁴²⁾ made a study in which trans-scleral autologous blood was injected in the subretinal space of 34 rabbits. Twenty hours later, tPA was injected in the posterior vitreous of 24 eyes and saline solution in 10 eyes as controls. Subretinal blood lysis was evaluated by ophthalmoscopy and retinal function was assessed by electroretinography. In the eyes in which tPA was injected, a disappearance of the formed clot was seen at the 24 hours, and all the blood disappeared after 6 days. On the contrary, in the group with saline solution, the clot did not show modifications at 24 hours or even 3 days later. The presence of blood in the subretinal space caused an important reduction in the electroretinogram amplitudes both in the tPA group and in the control group. With these results, the authors concluded that although tPA application made a rapid clot lysis, it could not prevent retinal damage registered by electroretinography. Similar results were reported by Ibanez et al in humans. They reported the surgical results of 47 patients who presented subretinal hemorrhage.⁽⁴³⁾ In this study, the authors concluded that tPA addition in order to achieve clot lysis appeared not to have improved in a significant way the final visual acuity of the patients.



Surgical Technique for Evacuating Subretinal Blood

A three-port pars-plana vitrectomy is made and the posterior vitreous cortex removed. A useful way to achieve this separation is by means of the use of a flexible silicone tip in order to aspirate and thereby grasp the posterior vitreous surrounding the optic disc. Once vitreous occludes the tip, the aspiration pressure can be increased to 400 mm/Hg and a delicate movement made to completely separate the cortex up to the equatorial zone (Figure 7).⁽⁴⁴⁾ Another technique that we commonly use is by means of a vitreous cutter, using an aspiration pressure of 200 mm/Hg directly over the optic disc. In this way, it is possible to engage the posterior vitreous and then to detach it from the retina up to the equator. Once separated it is removed with the vitreous cutter. Although at the present time there are no reports that clearly show the advantages of vitreous cortex removal in these cases, it is probable that it diminishes the risk of secondary rhegmatogenous retinal detachment and PVR.

Next, a small retinal penetration is made with a 33-gauge, bent, sharp subretinal cannula (Infinitect, Chesterfield, MO) at one of the margins of the hemorrhage. It is important not to make this cut over the clot because in case it cannot be completely extracted, the neurosensory retina will not lie in complete apposition with the RPE, and that can allow a secondary retinal detachment.⁽⁴⁴⁾ If that instrument is not available, an MVR blade

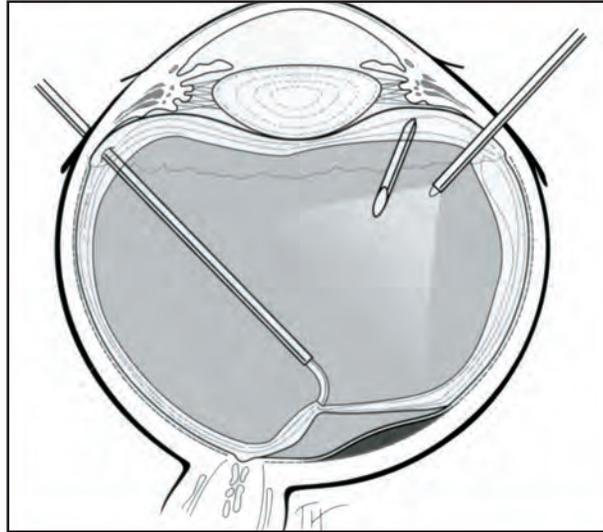
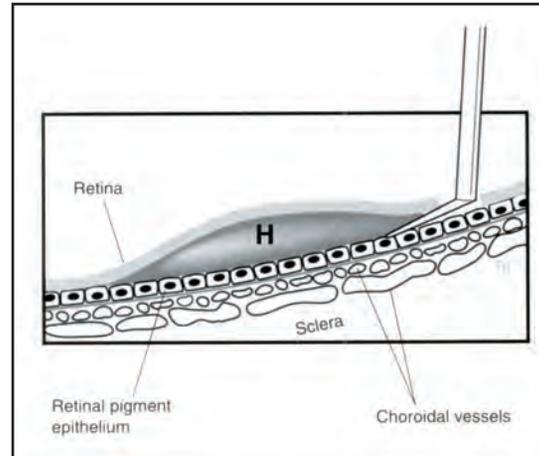


Figure 7: Removal of the posterior vitreous gel with a silicone-tipped extrusion needle with active suction. Bending of the silicone tip indicates that the tip is engaged in cortical vitreous.

can be used perfectly if the tip is bent approximately 3 mm (Figure 8). The angle of this bend will depend on the entrance site: if the hemorrhage is located in the posterior pole, it will be a 130-degree bend and if the hemorrhage is extended to more peripheral areas it must be bent to 90 degrees.

The retinal perforation is commonly made in the temporal side, but it can be made in the superior or inferior areas of the macula depending on the surgeon's preference for each case in particular. We prefer to raise the infusion bottle to increase momentarily the intraocular pressure, watching pulsations of the central retinal artery. This can limit the risk of bleeding when penetrating the undiathermized retina.

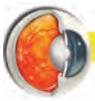
Figure 8: Perforation of the neurosensory retina with an angled spatula. The retinotomy site is adjacent to the subretinal hemorrhage (H).



If the hemorrhage is recent (<10 days) tPA can be applied in order to facilitate the clot extraction. In this case, it is ideal to use the bent 36-gauge cannula that is placed on a 1 ml syringe (tuberculin syringe) containing tPA at a concentration that can vary from 6.25 $\mu\text{g}/0.1$ ml to 25 $\mu\text{g}/0.1$ ml. per 0.1 to 0.3 ml, injecting the tPA under the neurosensory retina⁽²³⁾. Attention must be paid to inject directly in the interior of the clot and not contiguous to the retina or the RPE to avoid damage to cellular components. Generally the assistant injects the tPA while the surgeon pays attention so that it is injected to the interior of the clot. Occasionally it is necessary to move the cannula in order to set it in other sites in the clot. The advantage of the 33-gauge, bent, sharp, subretinal cannula is that it makes a small entrance by which

tPA does not escape from the subretinal space. Next, it is necessary to wait from 30 to 45 minutes so that tPA can lyse the clot. Scleral plugs are placed into the sclerotomy sites, and the eye is left with no movement in order to avoid tPA reflux in to the vitreous cavity. An alternative to this step is to wait only 15-20 minutes and later to irrigate and aspirate the blood, and then re-inject tPA and wait another 15-20 minutes.⁽⁴⁴⁾

After sufficient time, the scleral plugs are removed and a final washing of the blood is done. There are different ways to do this. Lewis has designed a dual-barrel infusion-aspiration handpiece⁽³⁸⁾ (Infinitech, Chesterfield, MO) that makes this maneuver easier. With this instrument, the surgeon extracts the lysed blood using very low active aspiration while



the assistant slowly irrigates. It is important to pay attention that the retinal dome does not collapse to avoid the possibility of additional photoreceptor damage. Commonly there does not exist a total lysis of the clot so it is necessary to leave some remnants of the hemorrhage in the subretinal space.

In cases in which tPA is not used, retinal penetration can be made with an MVR blade tip. Next an oblique cut of approximately 120-150 degrees to the flexible silicone tip that makes easier its slipping towards the subretinal space (Figure 9) is made, limiting the mechanical damage to the RPE. The silicon tip is connected to a backflush handle in order to make alternating suction and backflush-

ing (Figure 10).⁽⁴⁵⁾ It is possible in this way to wash away fresh or lysed blood. In the cases in which a solid clot is still present, it is possible to increase the suction in order to grasp it and pull it into the vitreous cavity. If this mechanism fails, subretinal forceps can be used. Occasionally it is necessary to widen the retinotomy in order to facilitate the clot passage. This can be done using vertical scissors following the horizontal raphe to reduce the risk of peripheral scotomas. Unless the cut is very extensive, it is not necessary to use diathermy to cauterize the retinal vessels. We frequently use a small bubble (1-1.5 cc) of perfluorocarbon liquid⁽⁴⁶⁾ that can facilitate the blood expression towards vitreous cavity making subretinal maneuvers less necessary.

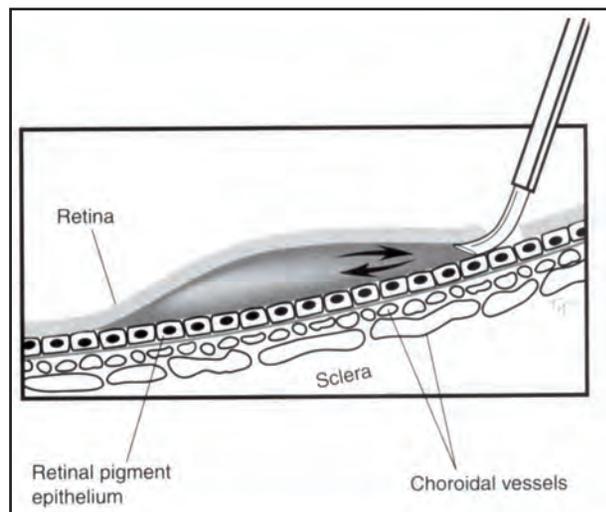
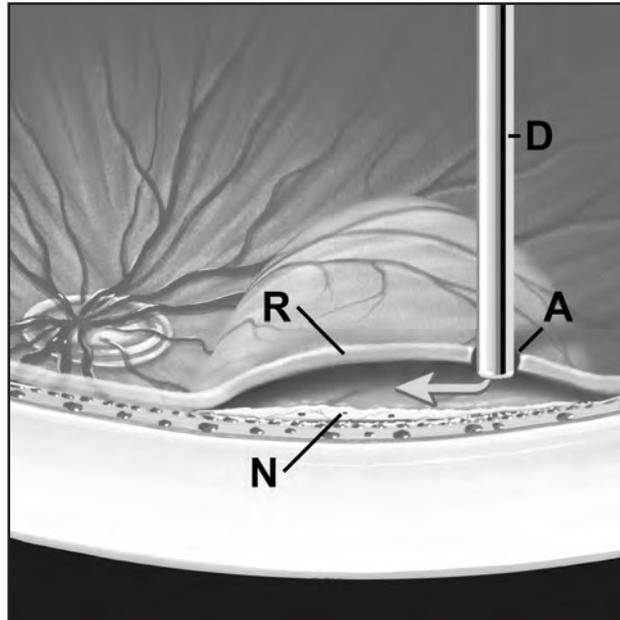


Figure 9: Silicone-tipped cannula with an oblique cut slides into the subretinal space. The oblique cut decreases damage to the RPE.

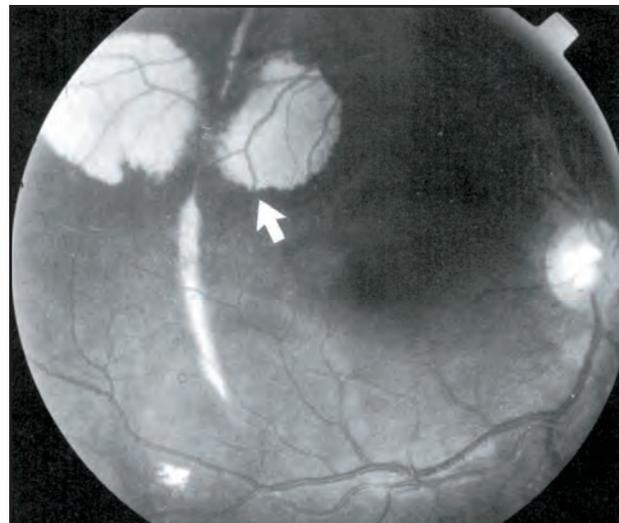


Figure 10: Alternating suction and back-flushing facilitates clearing of the subretinal hemorrhage.



As previously mentioned macular hemorrhages in trauma can be located in different levels, so it can happen that part of the blood is localized in the retinal tissue. It is important to recognize these variants in these cases, because the surgeon must limit himself to attempting to extract only blood localized between the neurosensory retina and the retinal pigment epithelium. In patients who present with hemorrhages older than 7 days, it is possible to see a yellowish change in the color of the blood (Figure 11).⁽⁴⁷⁾

Figure 11: Fundus photograph of a young man who sustained blunt trauma to the right eye 20 days before. There is a choroidal rupture with a secondary subretinal hemorrhage (arrow).





After extracting the subretinal blood, the peripheral retina is inspected looking for holes or tears. In case any are found, we apply cryotherapy to the lesions. The placement of a scleral buckle is not necessary.

Finally a complete air-fluid exchange is made (Figure 12). The application of endolaser burns is not necessary unless the retinotomy is extensive and the surgeon considers there is a risk for retinal detachment. If the eye is phakic, we generally use a non expandable concentration of SF_6 (18%). In aphakic or pseudophakic eyes we use 14% C_3F_8 . Some authors have reported the use of air only, without an expandable gas mixture for postoperative tamponade.⁽²³⁾ Finally, the sclerotomies are sutured.

Postoperatively, the fundus is evaluated to detect the presence of recurrent bleeding. Remaining blood remnants generally disappear after 2 weeks. As the gas bubble disappears, the peripheral retina must be carefully observed looking for subretinal fluid that can mean a tear or a peripheral hole. Visual acuity tends to improve after the first or second postoperative month (Figure 13a-c).

It is very important to discuss preoperatively the risk/benefit ratio of this surgery with the patient and his family. The more frequent complications of this kind of surgery include retinal detachment and postoperative cataract formation. Retinal detachment has been reported mainly in the cases in which extensive retinotomies were necessary.^(31,33)

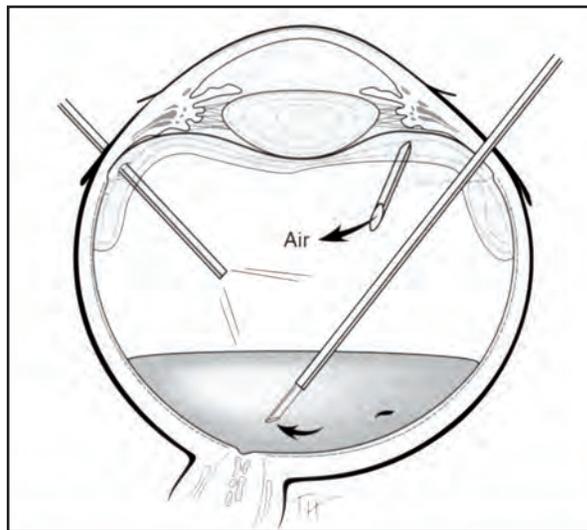


Figure 12: Fluid-air exchange is performed by aspirating over the optic disc. There is no need to aspirate the remaining subretinal fluid on this area.

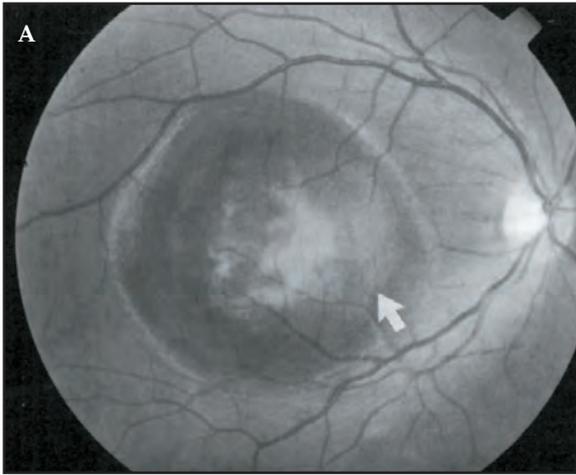
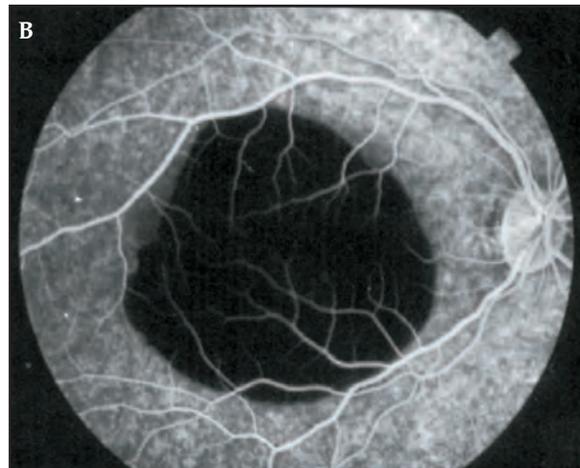


Figure 13: (A): Clinical photograph taken 6 days after blunt ocular trauma. There is an extensive subretinal hemorrhage that produces significant elevation of the retina. There are some yellow changes in the coloration of the blood (arrow). The visual acuity is counting fingers at 3 feet. (B): Preoperative fluorescein angiogram of the same case showing blocked fluorescence and no evidence of choroidal rupture. (C): Postoperative appearance at 3 weeks. Retinotomy is situated superotemporal to the macula with associated mildly disturbed RPE. There is a choroidal rupture located away from the center of the macula. Intraretinal material is still present. Visual acuity has improved to 20/60 at this examination.





Lewis⁽³⁸⁾ suggests that tPA usage can decrease the presence of retinal detachment due to the smaller retinotomy that is necessary in these cases. Nevertheless, Moriarty⁽⁴⁸⁾ reported retinal detachment in 13% of the operated cases (15 patients) still with the usage of tPA. Cataract formation is a complication of vitrectomy, and is more frequent in patients older than 50 years of age.

McCannel et al⁽⁴⁹⁾ has reported the case of a patient in which choroidal neovascularization formation appeared in the retinotomy site made for the surgical removal of a neovascular membrane.

TRAUMATIC SUPRACHOROIDAL HEMORRHAGE

Suprachoroidal hemorrhage (SCH) is defined as an accumulation of blood within the space between the choroid and the sclera (known as the suprachoroidal space).⁽⁵⁰⁾ While normally a potential space, holding a very little amount of fluid (approximately 10 μ l), it becomes a true space when filled with fluid or blood, with the scleral spur and the border of the optic disc as its anterior and posterior boundaries, respectively.⁽⁵¹⁾

Suprachoroidal hemorrhage may have different etiologies, such as blunt trauma, penetrating trauma, or intraocular surgery, the latter being the most frequent cause.^(50,51) This chapter will deal with traumatic SCH, which behaves differently from intraoperative or postoperative SCH, although they share some characteristics. Furthermore, most published

data about the management of this entity deals with SCH associated to intraocular surgery, and must sometimes be transpolated to the management of traumatic SCH.

Pathophysiology

Traumatic events may precipitate SCH by two means:

1. A mechanism unique to penetrating trauma: Trauma with an object that penetrates through the sclera, directly damaging the choroidal vessels, which in turn bleed into the suprachoroidal space, causing a SCH.
2. A mechanism analogous to the one that precipitates SCH associated to intraocular surgery: Penetrating trauma to the anterior or posterior segment may cause the loss of intraocular fluids or tissue, leading to hypotony, which has been deeply implicated in the genesis of SCH. The exact mechanism by which hypotony causes SCH is unclear, but studies have shown the rupture of a necrotic long or short posterior ciliary artery after hypotony.⁽⁵²⁾ In a rabbit experimental model of expulsive hemorrhage, in which the central cornea, lens and anterior vitreous were removed, four stages in the development of SCH were described: 1) Engorgement of the choriocapillaris, (2) Suprachoroidal effusion, mainly near the posterior pole, (3) Stretching and tearing of the choroidal vessels as the effusion enlarged, and (4) Massive extravasation of blood into the choroidal space.⁽⁵³⁾ These findings suggest that hypotony and/or the loss of intraocular tissue, by this mechanism, lead to a chain of events that culminates in SCH.



The genesis of SCH in closed blunt trauma is even less clear, since in theory, intraocular pressure may limit the extent to which the hemorrhage may increase in size. However, it is possible to observe very large SCH in cases in which trauma is purely blunt, without loss of intraocular tissue and/or hypotony. It has been hypothesized that since blunt trauma modifies the shape of the globe (anteroposterior shortening and equatorial expansion),⁽⁵⁴⁾ shearing forces are generated that tear and rupture the choroidal vessels, causing SCH.

Diagnosis

Suprachoroidal hemorrhage may be visible by ophthalmoscopic evaluation of the fundus, when the media are transparent enough to do so, in which case it appears as an elevated dome-shaped lesion or lesions at the level of the equator, and sometimes extending posteriorly; they can be small in size (known as “limited” SCH) or very large, with contact of the inner retinal surface of the lesions (known as “kissing”, “appositional” or “massive” SCH).

In most cases, however, traumatic damage to ocular structures (such as corneal opacities, vitreous or anterior chamber hemorrhage, or cataract) makes clinical evaluation of the fundus impossible, in which case ocular ultrasound images are extremely useful.⁽⁵⁵⁾ Ecographic evaluation of a traumatized eye with media opacities must be done as soon as possible in order to evaluate intraocular structures. This procedure can be performed through the lids in eyes with suspected penetrating injury, or directly on the ocular surface.

Ultrasound can give information about the presence of vitreous hemorrhage, retinal detachment, intraocular foreign body, and/or SCH, as well as their extent and localization. Furthermore, it can differentiate if the contents of a choroidal detachment are hemorrhagic or serous in nature. In cases of SCH, a dome-shaped separation of the choroid from the sclera is observed, and the suprachoroidal space is filled with hyperechoic signals denoting the presence of blood.

Ultrasound is also a very valuable tool for the evaluation of the liquefaction of suprachoroidal blood, which is of paramount importance to plan a drainage surgical procedure, since the blood must be liquefied in order to be drained. Early after trauma, suprachoroidal blood is seen as hyperechoic signals of irregular internal structure, indicating the presence of a disorganized clot (Figure 14). After some days, the intensity of the signals is lower and more regular, indicating the beginning of liquefaction (Figure 15). After more days, the ultrasound image of suprachoroidal blood is homogenous, with low-reflective mobile opacities.⁽⁵⁵⁾ The time from the appearance of SCH to liquefaction has been reported to be between 7 and 14 days.^(51, 54-58)

Computed tomography^(59, 60) and magnetic resonance imaging^(61, 62) have also been found of aid in the diagnosis of SCH, allowing even for the differentiation between serous and hemorrhagic content, as well as other features. However, the amount of information that can be obtained from these diagnostic studies is still limited when compared to ultrasound. Furthermore, magnetic resonance



Figure 14: Ultrasound B-scan showing a shallow suprachoroidal hemorrhage, one day after trauma. Note that the contents of the choroidal detachment are hyperechoic and heterogeneous in nature, indicating the presence of clotted hemorrhage.

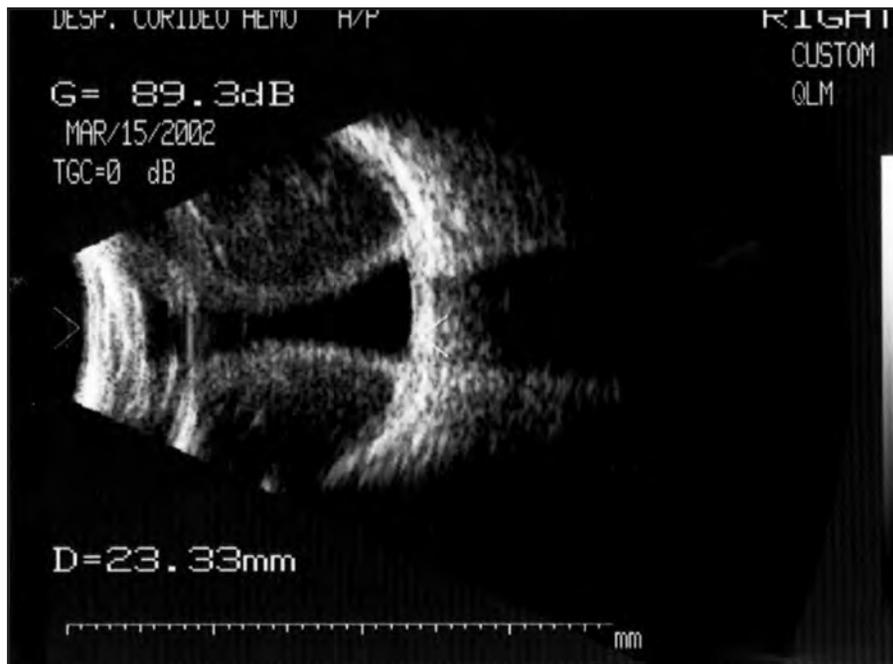


Figure 15: Ultrasound B-scan showing a large suprachoroidal hemorrhage without apposition, 5 days after trauma. Note that the contents of the choroidal detachment are less heterogeneous than the ones in figure 14, indicating the beginning of clot liquefaction.



imaging is contraindicated in cases where a metallic foreign body is suspected.

Management

Management of traumatic SCH is somewhat similar to the management of intraoperative or delayed SCH. In fact, most of the criteria and techniques applied to the management of traumatic SCH must be transplanted from information available from non-traumatic SCH. The management of traumatic SCH depends on several factors, including the need to manage other lesions in the traumatized eye, the extent of the SCH (limited vs massive), and characteristics of the hemorrhage (solid clot vs liquefied hemorrhage).

Indication for Surgery

Limited or localized SCH (sometimes called suprachoroidal hematoma) most of the times does not require any surgical management, since the blood clot will liquefy and reabsorb in the matter of weeks (Figure 14).⁽⁶³⁾ If a patient needs surgical management for other ocular lesions, (e.g. cataract, retinal detachment, etc), no surgical maneuvers are performed to drain the SCH, since these maneuvers themselves may cause more damage to the eye.

Indications for surgical drainage of traumatic SCH include appositional configuration, and other indications for vitreo-retinal surgery not directly related to SCH,

such as the presence of retinal detachment (Figure 16), vitreous hemorrhage, intraocular foreign body, retained lens material, etc, in which the size of the SCH is so large as to limit the intraoperative maneuvers.

The presence of appositional configuration has been traditionally regarded as the main indication for SCH drainage (Figure 17), since it has been reported that adherence of the retina may occur after apposition.⁽⁶⁴⁾ This view, however, has been challenged by other authors, who followed clinically and ecographically the natural history of appositional SCH of various etiologies in 18 patients, and found that apposition lasted for 10 to 25 days, and after that the hemorrhage reabsorbed without any sign of persistent retinal adherence.⁽⁵⁵⁾

Regardless of the presence or absence of persistent retinal adherence, appositional configuration has been found in other studies to be a sign of bad prognosis. Reynolds et al reported the outcome of 20 eyes with appositional SCH.⁽⁵⁷⁾ Thirteen of these eyes underwent surgical drainage while the rest remained in observation. Forty six percent of the eyes that underwent surgery achieved visual acuity of 20/200 or better, compared to 0% of the ones that had no intervention. Scott et al reported a study in 51 eyes with appositional SCH, and found a negative correlation between duration of apposition and final visual acuity.⁽⁶⁵⁾ Other studies, although performed on postoperative rather than traumatic SCH, found that the presence and duration of apposition resulted in worse prognosis.^(66,67)

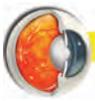


Figure 16: Ultrasound B-scan showing a medium-sized suprachoroidal hemorrhage (above) associated to a funnel-shaped retinal detachment (below).

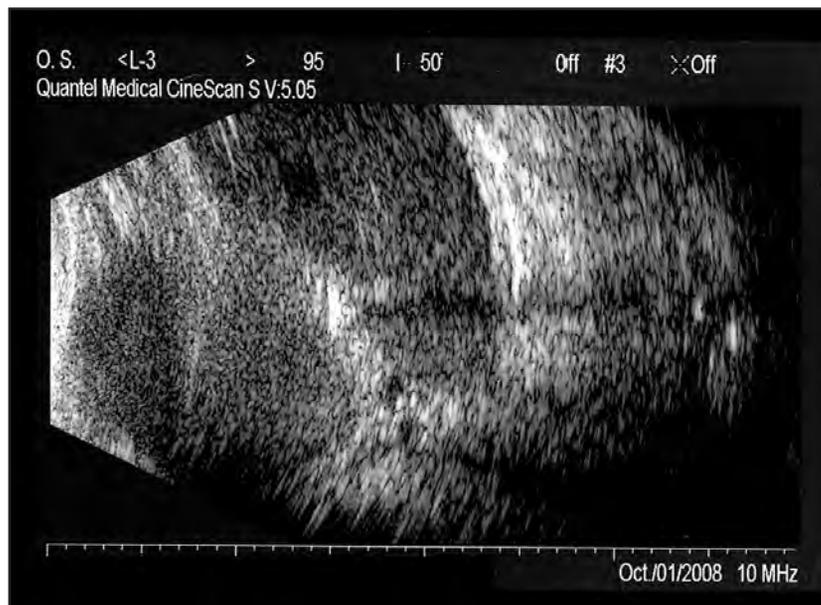


Figure 17: Ultrasound B-scan showing an appositional suprachoroidal hemorrhage, and the presence of an intraocular foreign body with acoustic shadow between the two dome-shaped lesions.



Timing of Intervention

The timing between the appearance of SCH (which usually is the time of the traumatic event) and the surgical drainage is of paramount importance, since during the first days after trauma, blood within the suprachoroidal space is forming a clot,⁽⁵⁵⁾ which is very difficult to drain through a sclerotomy. Most authors agree that surgical drainage must be delayed 7 to 14 days or until ecographic evidence of clot lysis.

If other procedures (such as wound closure, etc) need to be urgently performed in a traumatized eye that also has considerable SCH, the drainage of the SCH must be delayed, since most attempts to drain a SCH before it has liquefied are usually unsuccessful, and surgical maneuvers to this effect most often result in further damage to the globe.⁽⁵¹⁾

Surgical Technique

Traumatic SCH is frequently associated to posterior segment pathology, such as vitreous hemorrhage, retinal detachment, subretinal hemorrhage, luxated lens or lens fragments, intraocular foreign body, retinal incarceration in the wound, etc., that need to be addressed during the same surgical procedure. For this reason, most of the times its management requires a vitreoretinal approach.

The first surgical objective is to create a drainage sclerotomy. The placement of the sclerotomy is very important, and should be placed in a quadrant where the SCH is largest,

in order to avoid damage to the inner choroid or to puncture the retina. The sclerotomy is usually created at approximately 6 mm behind the limbus with a 20G MVR blade, and can be orientated perpendicular or parallel to the limbus. A well-placed sclerotomy in an eye with a well-liquified SCH should result in immediate egress of suprachoroidal blood through the sclerotomy. The blood should be purple-brown in color (Figure 18).

The second surgical objective is to pressurize the vitreous cavity, and this can be achieved in several ways, depending on the extent of the SCH:

1. **Anterior chamber infusion:** If there is a very large SCH that totally precludes a pars plana incision, an infusion must be placed in the anterior chamber. This can be done by creating a clear corneal incision with a 15° blade, and placing an anterior chamber maintainer or a 23G infusion cannula. Since most patients are pseudophakic or aphakic, balanced saline solution (BSS) freely flows to the vitreous cavity. This can also be done, however, in phakic patients, since BSS can also flow through the zonular ligaments, although sometimes the anterior chamber deepens before this happens, resulting in zonular weakness (Figure 19).
2. **Pars-plana infusion:** If the SCH is limited to some quadrants, one quadrant may be available for the placement of a pars plana infusion, 3 to 4 mm behind the limbus, using a 6 mm infusion cannula. This procedure, however, carries some risks. In the presence of SCH, the pars plana, retina and vitreous base are not in their normal

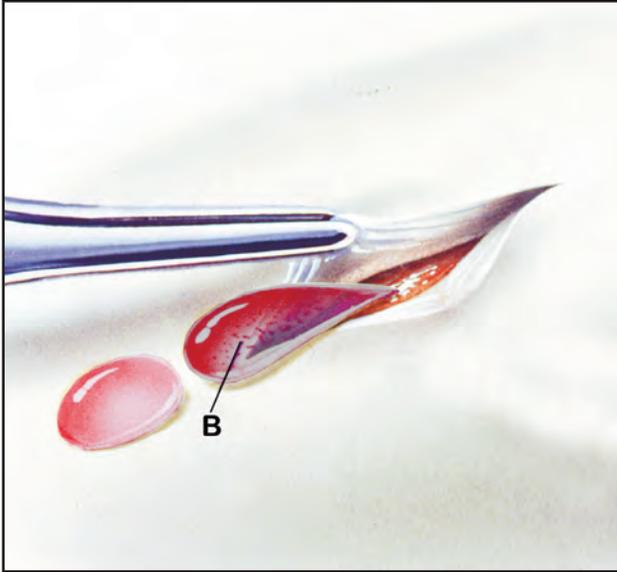


Figure 18. Draining suprachoroidal blood (B) through the sclerotomy. (Art from Jaypee - Highlights Medical Publishers).

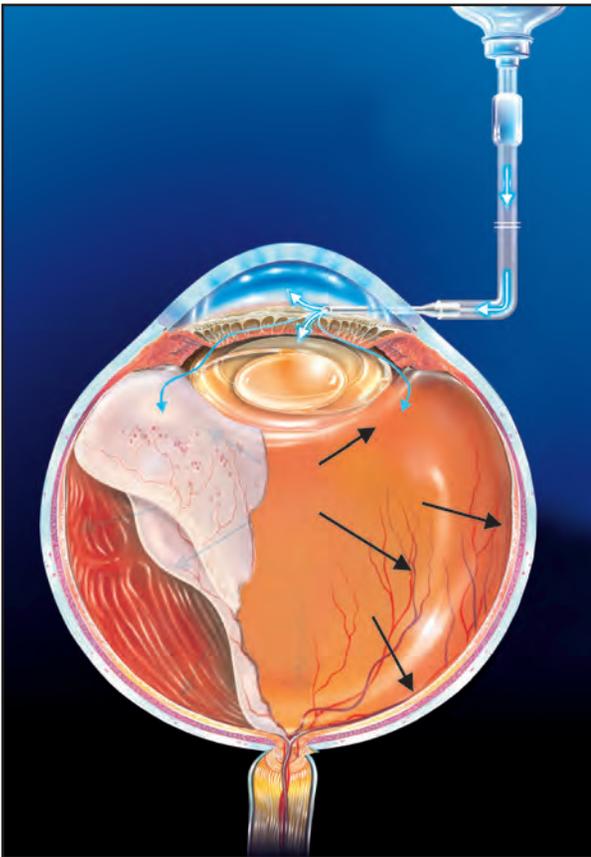


Figure 19. Pars Plana Infusion. Collocation of anterior chamber infusion. Free flow of BSS is permitted from anterior to posterior chamber. (Art from Jaypee - Highlights Medical Publishers).



anatomic location, and may be damaged when attempting to create a surgical access. The other risk, even if there is a quadrant or quadrants without SCH, is to damage the retina contralateral to the sclerotomy if the SCH is very large.

It is not uncommon when creating a pars plana access, that the SCH starts draining through this sclerotomy, even if it is this anterior. In cases where blood (and not vitreous) comes out of the wound, it is usually difficult to insert the cannula in the vitreous cavity, adding the risk of suprachoroidal infusion of BSS, which will make the problem even worse. To overcome this problem, a light pipe may be used (an endlight probe coupled with infusion).

Once the vitreous cavity is pressurized, either by an anterior chamber or pars plana infusion, the pressure forces the SCH out through the posterior sclerotomy. It is sometimes necessary to depress one lip of the wound to facilitate the egress of blood, and sometimes of tiny blood clots. The drainage should be continued as much as possible, until no more blood is observed to come out of the sclerotomy. At this time it is important to examine the fundus with indirect ophthalmoscopy, to assess the size of the remaining hemorrhage. If a substantial hemorrhage remains, it is advisable to create a new drainage sclerotomy or sclerotomies, until most of the hemorrhage has been drained. It is important to note that most of the times a complete drainage cannot be achieved, and small "islands" of suprachoroidal blood remain, that later will reabsorb spontaneously in the matter of weeks.

Once the suprachoroidal blood has been drained, a standard three-port pars plana vitrectomy procedure can be performed in order to address the rest of the vitreoretinal pathology. Depending on the surgical findings, other procedures such as endophotocoagulation, endodiathermy, the use of perfluorocarbon liquids, removal of intraocular foreign body, retinotomy, retinectomy, air/fluid exchange, and/or internal tamponade with gas or silicone may be needed.⁽⁶⁸⁾

It is important to note that when silicone oil is used as tamponade, most of the times there will be a remaining inferior fluid meniscus after a few weeks in the postoperative period, even though the silicone fill in the immediate postoperative period is complete. The explanation for this is, as mentioned above, that after SCH drainage there is always remaining blood in the suprachoroidal space, that will reabsorb during the following weeks, leaving room in the vitreous cavity for the fluid meniscus.

Prognosis

Despite modern vitreoretinal surgical techniques, visual outcomes of eyes with traumatic SCH are modest at best. It is difficult to assess the prognosis of traumatic SCH since most publications group it with intraoperative and postoperative SCH. Reynolds et al reported 106 patients with SCH, out of which 35 were due to trauma. Factors for bad prognosis included the presence of retinal detachment and SCH affecting the four quadrants. Thirty four percent of the patients undergoing a surgical procedure



achieved visual acuity of 20/200 or better.⁽⁵⁷⁾ Wirostko et al reported a study on 48 eyes with SCH, 16 of which were secondary to trauma. They classified SCH in four categories: 1) Non-appositional choroidal hemorrhage without vitreous or retinal incarceration; 2) Centrally appositional choroidal hemorrhage without vitreous or retinal incarceration; 3) SCH with associated vitreous incarceration in the wound, and 4) SCH with retinal incarceration in the wound. They found a higher probability of no light perception vision, persistent hypotony and irreparable retinal detachment with increasing SCH complexity, especially when retinal incarceration was present.⁽⁶⁹⁾ Other authors have published results about non-traumatic SCH, finding that predictors of poor final visual acuity were vitreous incarceration in the wound, retinal detachment, afferent pupillary defect, longer duration of apposition, and extension of the SCH to the posterior pole.^(65,66,67,70,71,72)

Conclusion

The presence of either traumatic subretinal hemorrhage or suprachoroidal hemorrhage means that severe damage has been done to the eye. Even with modern management and vitreoretinal surgical techniques at our disposal, visual prognosis in these cases is very limited, due to the delicate nature of the structures involved. The complex management of these pathologies requires skilled and experienced surgeons, and surgical facilities with the necessary vitreoretinal surgical tools at their disposal.

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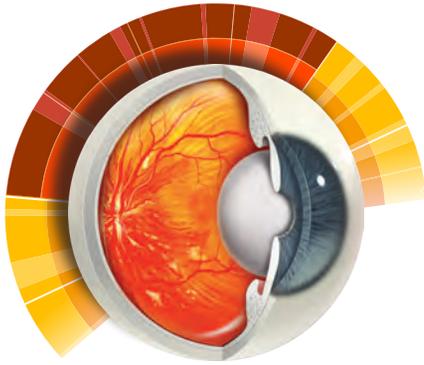
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34

Surgical Management of Proliferative Vitreoretinopathy

MARC J. SPIRN, MD.,
CARL REGILLO, MD.,
HILEL LEWIS, MD.

Proliferative Vitreoretinopathy (PVR) is currently the biggest obstacle to successful retinal reattachment surgery, accounting for approximately 75% of all primary surgical failures. PVR is characterized by growth and migration of preretinal or subretinal membranes. Contraction of these membranes causes foreshortening of the retina, leading to stretch holes or traction, which redetaches the retina. As the proliferation matures, the once compliant retinal tissue becomes rigid and immobile, making repair more difficult. In addition, patients with PVR-associated detachments often have extensive levels of visual loss. As technological advances in vitreoretinal surgery continue to move forward, effective new treatments for PVR continue to lag behind. Although anatomic repair is possible in greater than 90% of detachments with associated PVR, primary prevention of PVR remains an obstacle.¹

Causes of PVR

The main cause of PVR is the proliferation and contraction of cells in the periretinal surfaces and vitreous gel. First, the cells need to gain access to these locations, and then they need a milieu that will make them grow, proliferate, and contract. This milieu is sometimes created by the disease itself. In cases of retinal tear, pigment epithelial cells can already be dispersed into the vitreous. A retinal detachment also is associated with breakdown of the blood ocular barrier. The surgeon's attempts at intervention and repair can increase the likelihood of dispersing cells or making the milieu more suitable for these cells to grow and contract.

When the blood ocular barrier is broken, growth factors gain entrance into the eye.

These include fibronectin, a platelet-derived growth factor, and other growth factors that cause cells in the vitreous cavity or the epiretinal or retrolental surfaces to proliferate and contract. Retinal pigment epithelial cells can produce collagen, but only in the presence of some growth factors. Like the needed ingredients in a recipe, all these mechanisms together—cells, vitreous gel, growth factors—cause PVR.

Once periretinal proliferative membranes are in the vitreous gel, they exert a tractional force that will either reopen the original retinal break or cause new retinal breaks, with redetachment of the retina. The result will be a complicated, more difficult to repair rhegmatogenous retinal detachment.²

Risk Factors

The eyes most likely to develop PVR after retinal reattachment surgery are those with mild PVR prior to surgery. Other risk factors for PVR include excessive cryoretinopexy (Figure 1), retinal tears with greater than 3 disc diameters of exposed retinal pigment epithelium, previous vitrectomy, and postoperative choroidal detachments. Most rhegmatogenous retinal detachments can be complicated by some degree of proliferative vitreoretinopathy. Some patients with immunodeficiencies such as the acquired immunodeficiency syndrome (AIDS) develop mild PVR. Although one study has explored

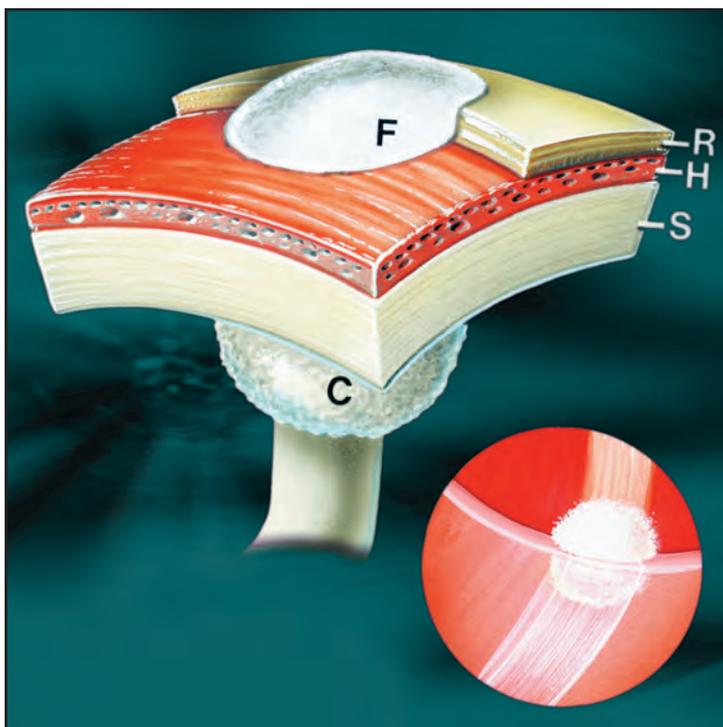


Figure 1: Excessive Cryoretinopexy as a Risk Factor for PVR. This conceptual view demonstrates improperly placed cryotherapy (C) to a retinal tear. The frozen area (F) has extended inside the tear rather than treating the edges of the retina (R) around the tear. This contributes to the release of retinal pigment epithelial cells and promotes the development of PVR. Choroid (H) and sclera (S). The magnified inset view shows the improper application at the edge of a retinal tear with cryotherapy. (A conceptual slit beam has been added to this illustration to enhance the 3-dimensional nature of the view.) The treatment should not extend into the base of the tear. Only neurosensory retina surrounding the tear should be treated. (Art from Jaypee - Highlights Medical Publishers).



risk factors using multivariate analysis, some other possible causes of PVR have not been studied. For example, the number of retinal tears present in an eye has not been studied as a risk factor for PVR.

In general, processes that increase vascular permeability are more likely to increase the probability of PVR formation. Specific risk factors that have been identified include: uveitis; large, giant, or multiple tears; vitreous hemorrhage, preoperative or postoperative choroidal detachments; aphakia; multiple previous surgeries; and large detachments involving greater than 2 quadrants of the eye.³⁻⁶

Classification: Anterior and Posterior Components

The type of surgical treatment indicated depends upon the type of PVR. PVR has two basic components: an anterior and a posterior component (Figure 2). Anterior PVR occurs anterior to the posterior border of the vitreous base. The types of tractional forces present at the vitreous base include anteroposterior, circumferential, and perpendicular. Anteroposterior traction is manifest

as anterior displacement of the posterior border of the vitreous base. With this type of anterior traction the posterior border of the vitreous base is displaced either to the anterior insertion of the vitreous base, or to the ciliary processes, the ciliary body, or, in severe cases, even to the pupillary margin. Anteroposterior traction is recognizable because the iris is retracted posteriorly and because there is a circumferential trough anteriorly at the vitreous base.

The term “proliferative vitreoretinopathy” was coined in 1983 by the Retina Society Terminology Committee. In 1989, the classification was amended by the Silicone Study Group before being most recently modified in 1991 to its current classification. Currently, PVR is divided into grades A, B, and C. Grade A is limited to the presence of vitreous cells or haze. Grade B is defined by the presence of rolled or irregular edges of a tear or inner retinal surface wrinkling, denoting subclinical contraction. Grade C is recognized by the presence of preretinal or subretinal membranes. Grade C is further delineated as being anterior to the equator (grade Ca) or posterior to the equator (grade Cp) and by the number of clock hours involved (1 to 12).⁷

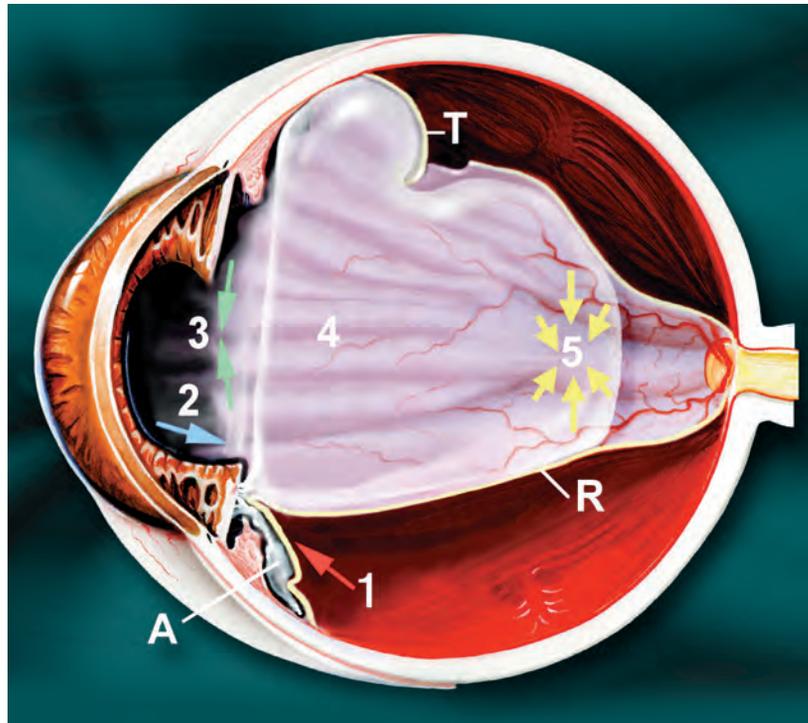


Figure 2: Anterior and Posterior Components of PVR. PVR has both an anterior and posterior component. Anterior PVR occurs anterior to the posterior border of the vitreous base. The types of tractional forces present at the vitreous base include anteroposterior, circumferential, and perpendicular. Anteroposterior traction is manifest as anterior displacement (1 - arrow) of the posterior border of the vitreous base. This traction is recognizable as the iris is retracted (2 - arrow) posteriorly, and there is a circumferential trough anteriorly in the vitreous base (A). Anterior circumferential traction is caused by proliferative tissue on the anterior and posterior vitreous surfaces, creating a ring (3 - arrows) at the posterior border of the vitreous base. It is recognizable by the occurrence of radial folds (4) in the retina that extend posteriorly from the posterior border of the vitreous base. Anterior perpendicular traction is caused by proliferative vitreous membranes (5 - arrows), particularly in the posterior vitreous hyaloid. It manifests clinically as an opacified and taut vitreous surface, causing an anterior funnel-shaped retinal detachment (R) as shown. Retinal tear (T). (Art from Jaypee - Highlights Medical Publishers).



Prevention

Although PVR cannot completely be prevented today, ophthalmic surgeons can take several steps to decrease the likelihood of its development.

Judicious Use of Cryotherapy

We as surgeons can judiciously use cryoretinopexy during repair of rhegmatogenous retinal detachment (Figure 3). The more cryotherapy used, the more likely is a breakdown of the blood ocular barrier as well as the dispersion of the retinal pigment epithelial cells into the vitreous cavity. Once these cells have entered the vitreous cavity, they are likely to proliferate and contract. Any treatment that minimizes the dispersion of retinal pigment epithelial cells into the vitreous cavity is likely to decrease the development of PVR. If cryotherapy is the selected treatment, only the minimum amount needed should be used, and the base of the retinal break should not be treated. Only the area surrounding the retinal break should be treated. This reduces the likelihood that pigment epithelium will migrate into the vitreous cavity.

Role of Laser Treatment

It is recommended that the surgeon minimize the breakdown of the blood ocular barrier. Some surgeons believe that laser

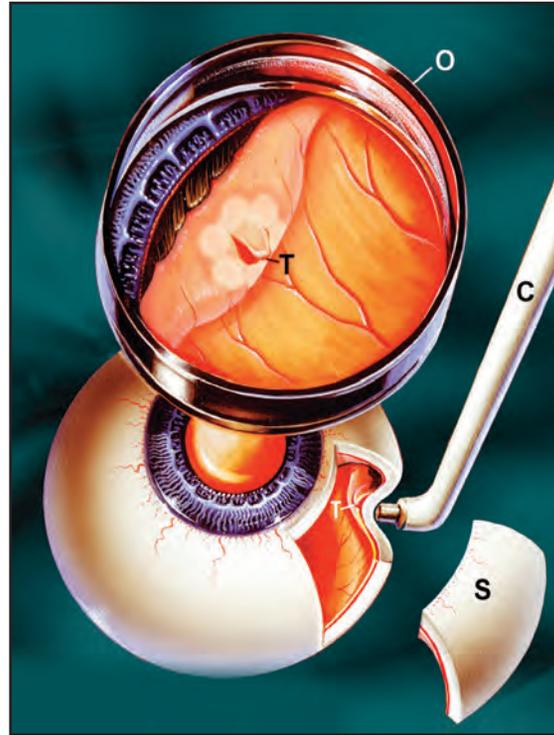


Figure 3: Judicious Use of Cryotherapy - Overall View. This internal/external conceptual illustration shows a cross section and corresponding surgeon's view of the final configuration of proper cryotherapy to a retinal break (T). Only the minimum amount of cryotherapy needed should be used. Only the area surrounding the retinal break should be treated, and the base of the break should not be treated. This reduces the likelihood that pigment epithelial cells will migrate into the vitreous cavity. View through ophthalmoscope (O). Cryoprobe (C). Portion of sclera (S) removed to reveal internal configuration. (Art from Jaypee - Highlights Medical Publishers).



treatment will create a chorioretinal adhesion decreasing the likelihood of breakdown of the blood ocular barrier. In order for the laser to take effect, the retinal break must already be closed. If subretinal fluid remains, it is more common to use initial cryotherapy.

Management of PVR

The current management of PVR primarily involves surgical remedy. Currently retinal detachments may be repaired using any of several techniques, including laser retinopexy, pneumatic retinopexy, encircling or segmental scleral buckling, or pars plana vitrectomy (PPV).

Laser retinopexy is a valuable technique that can be considered for limited detachments when there is no noticeable visual field loss. Benefits of laser retinopexy include patient convenience, no need for systemic anesthesia, and limited cost. Laser retinopexy may be effective treatment for retinal detachments with only grade A PVR, but is less likely to be successful when grade B or more PVR is present.

Pneumatic retinopexy likewise has the advantages of being an in-office procedure with less anesthesia-related morbidity. It can be utilized in patients with larger detachments but it is dependent on patient positioning and cooperation. Similarly, pneumatic retinopexy may be useful with detachments associated with grade A PVR, but it is less effective in the setting of grades B and C PVR.

Scleral buckling is frequently utilized when treating PVR detachments. Scleral buckles relieve both anterior-posterior traction and circumferential traction. This acts as an opposing force against which proliferative membranes must pull to redetach the retina. In the setting of PVR, encircling bands that support the entire vitreous base are more useful than segmental elements and are frequently used in conjunction with PPV. With milder degrees of grade C PVR, such as PVR limited to 1 quadrant, scleral buckling alone may be a viable option.⁸ This was similarly shown by Yao et al., who achieved high rates of anatomic success using scleral buckling alone in chronic detachments with PVR.⁹

Pars plana vitrectomy with or without scleral buckling remains the mainstay of surgical repair when PVR is present. One major advantage of vitrectomy over other surgical modalities is that it allows for removal of the inciting proliferative nidus. During surgical repair, vitreous cells can be removed, which may prevent these cells from progressing to further stages of PVR. Another obvious advantage of PPV over other treatment modalities is that PPV allows direct access to the proliferating membranes, which can be peeled during surgery. One disadvantage of PPV over other treatment modalities is that it may increase permeability of the blood retina/aqueous barrier more than other techniques.

Surgical Techniques

The goal of PVR detachment surgery is similar to traditional retinal detachment



surgery: treat all tears and relieve all traction. Several surgical techniques may enable more permanent anatomic success. After performing a core vitrectomy and meticulous peripheral dissection with 360° of scleral depression, attention is directed to the proliferative membranes. Intravitreal triamcinolone acetonide suspension may highlight these membranes.^{10,11}

The main surgical goals in managing PVR include closing the retinal breaks, sealing the retinal breaks, and completely releasing all periretinal traction. The technique used should minimize iatrogenic ocular complications and the recurrence of traction and achieve long-term stabilization of the attached retina. Mild cases of PVR should be treated with scleral buckling alone. Severe cases, however, require vitreoretinal surgery in addition to scleral buckling. The timing of surgery is controversial.

Although waiting for the periretinal membranes to mature makes the surgery technically easier, waiting has not been determined to improve the anatomic success rate. Since delaying surgery is likely to be associated with a worse visual result because the retina has been detached for a long period of time, earlier surgical intervention is indicated in cases of severe PVR. In these cases it is better to remove posterior membranes before anterior membranes whenever possible, stripping from the posterior pole toward the periphery in order to avoid disinserting peripheral retina. After membrane stripping is performed, perfluorocarbon liquid (PFCL) can be used to flatten the retina and to help identify areas of residual traction.

Surgery begins in the same way in all cases but changes depending upon whether the surgeon uses perfluorocarbon liquids. Initially, the surgeon places a scleral buckle. If the patient already has a scleral buckle, the scleral buckle is rarely revised. Then the pupil is managed with sutures, iris hooks or an expander pupil ring, which are only required if the pupil is small, miotic, or if the fundus cannot be well visualized anteriorly at the vitreous base. At this stage the lens must be managed. It is removed when it is opacified or when an anterior component is present even when the lens is clear. The posterior and anterior vitreous is removed with the help of scleral depression. If perfluorocarbon liquids are not used, anterior membrane dissection is followed by posterior epiretinal membrane dissection. Any subretinal membranes that exert significant traction and prevent the retina from re-attaching must be dissected (Figure 4).

Many surgeons believe that in cases of severe PVR, meticulous vitreous base dissection, removal of membranes, and, when necessary, a retinectomy are critical. Quiram et al reported functional and anatomic outcomes in patients with recurrent rhegmatogenous retinal detachments secondary to PVR.¹² In their series, patients who underwent radical anterior vitreous base dissection and lensectomy and patients who underwent inferior retinectomy had the highest success rates. Similarly, Tseng et al evaluated the utility of relaxing retinectomies in PVR detachments. They found that retinectomies were most useful when used in conjunction with silicone oil tamponade but added little additional benefit when combined with gas tamponade.¹³

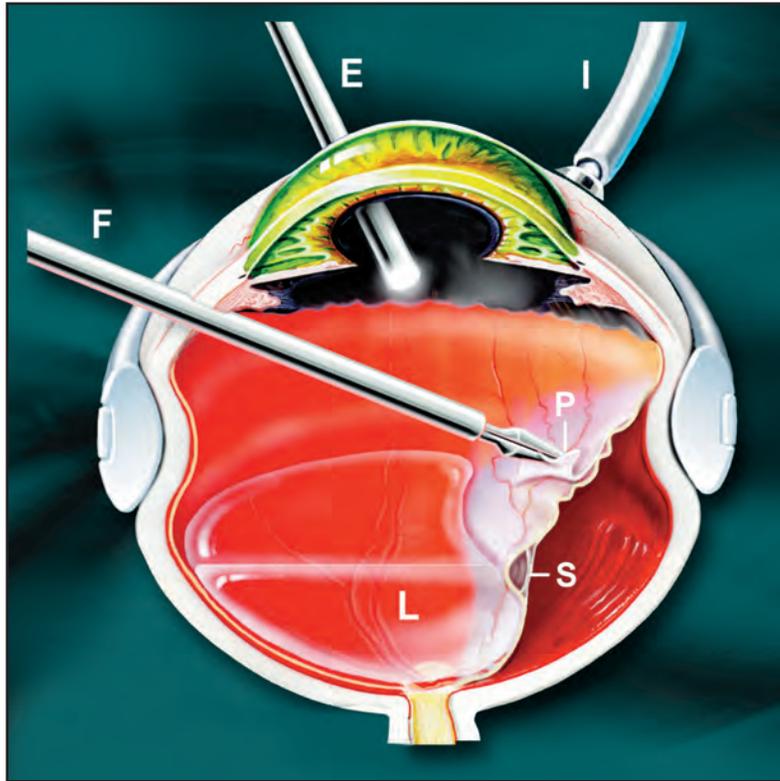


Figure 4: Surgical Treatment of PVR - Stage 2. Perfluorocarbon liquid (L) is injected. This will reveal any persistent traction from epiretinal membranes (P) which must be removed. A vitreoretinal pic or Grieshaber mini-diamond forceps (F) is used to remove such a membrane (P). Note subretinal membrane (S). Endoilluminator (E) and infusion terminal (I). (Art from Jaypee - Highlights Medical Publishers).

An important surgical factor that may determine the likelihood of success is the type of tamponade. The Silicone Study compared silicone oil with either sulfur hexafluoride (SF_6), or perfluoropropane (C_3F_8) in eyes with severe PVR.¹⁴⁻¹⁶ The Silicone Study suggested that silicone oil was more effective than SF_6 , but approximately equivalent to C_3F_8 in cases of severe PVR. Conversely, Quiram et al

noted that patients who received silicone oil had better attachment rates than did patients who received gas tamponade.

If the use of silicone oil is planned, an inferior iridectomy is made prior to performing a fluid/air exchange. The vitreous base is again inspected with additional anterior dissection if required. Endophotocoagulation



is used to treat preexisting and iatrogenic retinal breaks (Figure 5). The procedure is concluded with placement of an intraocular tamponade, either perfluoropropane gas or silicone oil.

One major drawback of conventional tamponades, ie, SF_6 , C_3F_8 , and silicone oil, is that they have limited exposure to the inferior retina over time. Because gravity causes most of the proliferative mediators

to settle in the inferior retina, PVR is most common inferiorly. Ability to more effectively tamponade the inferior retina may prevent these recurrences. Recently some investigators have sought to more adequately tamponade the inferior retina using agents that are heavier than water. Berker et al used a heavy silicone oil, Oxane HD (Bausch & Lomb, Rochester, NY), and they found that doing so increased their anatomic success with an acceptable complication profile.¹⁷

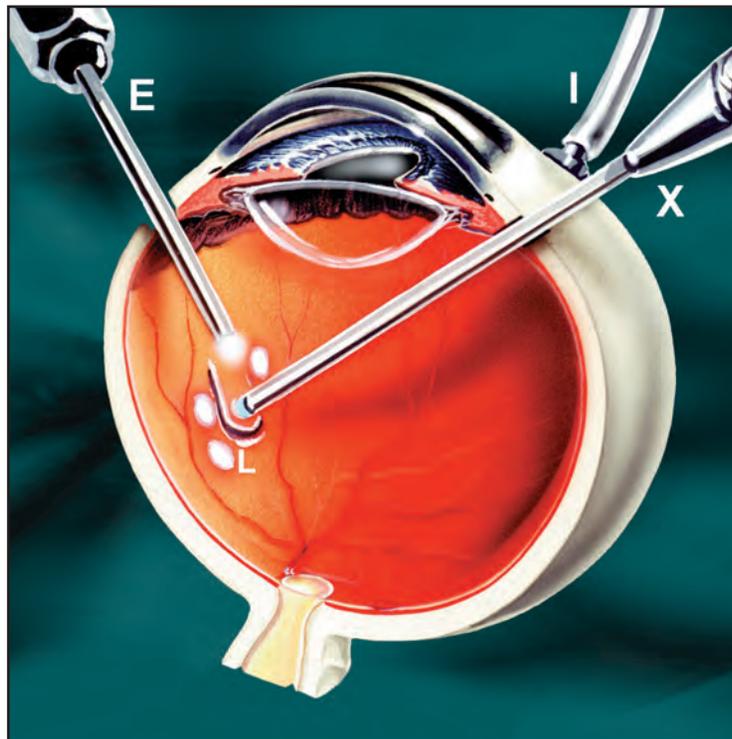


Figure 5: Surgical Treatment of PVR - Endophotocoagulation of Retinal Breaks. Endophotocoagulation is used to treat pre-existing and iatrogenic retinal breaks in eyes with PVR. The edges of the tear are treated (L) with the endolaser probe (X). Endoilluminator (E). Infusion terminal (I). (Art from Jaypee - Highlights Medical Publishers).



Posterior PVR

When all anterior traction has been released, the posterior retina is mobilized by dissecting the posterior membranes currently with endodrainage of subretinal fluid. The posterior epiretinal dissection is very important in order to release the posterior traction and allow the posterior retina not only to reattach intraoperatively but also to remain re-attached after the intraocular tamponade is either reabsorbed or removed from the eye.

According to Hilel Lewis, he prefers to use a bimanual technique with small-tip diamond forceps in one hand and a bent light pick in the other hand. Membrane dissection is started posteriorly at the optic nerve head, and epiretinal membranes are also engaged in the center of the star folds and gently stripped anteriorly. If the epiretinal membranes cannot be removed with a small-tip diamond forceps, he may use a bent myringotomy blade to engage the fine epiretinal.

Equatorial epiretinal membranes are frequently difficult to visualize. In cases in which equatorial traction is still present, perfluorocarbon liquids may identify residual epiretinal membranes that can be removed. Perfluorocarbon liquids should not be injected over a retinal break that is still under traction since the perfluorocarbon is likely to migrate into the subretinal space. However, if the traction has been released, it is possible to carefully and slowly inject the perfluorocarbon liquid over the retinal break, thereby stabilizing the

posterior retina and allowing for dissection of the anterior membranes.

Reoperations

Finally, reoperations after proliferative vitreoretinopathy repair are common. The most common indications for additional surgery include corneal opacification, cataract formation, recurrent retinal detachment with or without PVR, macular pucker, and silicone oil removal. One indication that is becoming more frequent is the development of hypotony despite retinal reattachment. Some patients after PVR surgery have total retinal reattachment or reattachment posterior to the scleral buckle but have very low intraocular pressures. If they are not treated, these eyes frequently progress to atrophía bulbi with shrinkage despite retinal reattachment. One of the causes of this hypotony is epicyliary proliferation. One of the causes of epicyliary proliferation is a massive output of fibrin, which is then deposited over the ciliary body. Cells are deposited on a scaffold made of fibrin matrix, and they contract and cause dysfunction of the ciliary body epithelium. In those cases the epicyliary proliferative membrane is dissected. If it is done earlier or soon after surgery, the intraocular pressure may increase and prevent atrophía bulbi. Surgery is not really designed to improve visual function because these patients already have an attached retina, but to decrease the likelihood of developing a blind and painful eye.



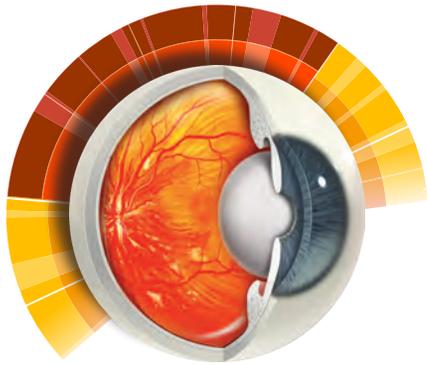
During the last several years the ophthalmic industry has produced some tremendous technological advances in vitreoretinal surgery. Surgical instruments have become smaller, enhancing patient postoperative comfort and enabling transconjunctival sutureless surgery. PVR continues, however, to hamper successful retinal detachment surgery. To improve our success rates after retinal detachment, we must find ways to limit the production and proliferation of PVR, either through pharmacologic means or enhanced surgical techniques.

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Vitreoretinal Surgery for Epiretinal Membranes

JAVIER A. MONTERO, MD, PhD.,
JOSE M. RUIZ-MORENO, MD, PhD.,
MARTA FERNÁNDEZ-MUÑOZ, MD, PhD.,
PEDRO AMAT-PERAL, MD.

Introduction

Epiretinal membranes (ERM) are defined by the appearance of a more or less transparent avascular fibrous tissue which is adhered to the internal layers of the retina in the macular area. This entity has been referred to under different terms such as primary retinal folds, secondary retinal gliosis, cellophane maculopathy, vitreoretinal juncture-simple epiretinal membranes, macular pucker, astrocytic epiretinal membranes, and epimacular proliferation, among others. ⁽¹⁻⁸⁾ Even though ERM may appear associated to certain vascular or inflammatory pathologies of the retina or following rhegmatogenous retinal detachment surgery, the most frequent scenario is that of primary ERM appearing in eyes that have not suffered diseases previously, in up to 80% of the cases. ⁽⁹⁻¹¹⁾

Idiopathic ERM may show a variable degree of adhesion to the macular retina and eventually cause retinal involvement with distortion of temporal vascular arcades and the appearance of foveal macular oedema.

ERM may eventually resolve and separate spontaneously from the retina. However, this event takes place rarely and most of the membranes will remain stable after an initial period of growth. ERM tend to remain unchanged and vision rarely improves or worsens dramatically. Presently, the only accepted procedure to remove ERM causing significant vision loss is vitreoretinal surgery, even though new advances are being made on other less aggressive, pharmacological therapies.

Vitreotomy is reserved for the cases of fast evolution with visual deterioration or threatening central vision.



Epidemiology

The prevalence of ERM is high. Klein et al reported a prevalence of 11.8% according to the Beaver Dam Eye Study.⁽¹²⁾ The association of ERM with age is clear and more than 90% of the patients are older than 50 years.^(6,13) The Blue Mountains Eye Study (BMES) reported a prevalence of 7% on a population 49 years of age or older on the basis of detailed eye examination and stereo retinal photography, and was found to be bilateral in 31% of the cases. The prevalence was 1.9% in persons younger than 60 years of age, 7.2% in persons 60 to 69 years of age, 11.6% in persons 70 to 79 years of age, and 9.3% in persons 80 years of age and older, with slightly higher rates in women. This study identified an early form without retinal folds, termed “cellophane macular reflex” (which was present in 4.8%), and a later stage with retinal folds, termed “preretinal macular fibrosis” which was significantly associated with diabetes and had a small, significant effect on visual acuity (VA) in 2.2% of the population. ERM was more frequent among persons who had undergone cataract surgery (16.8%), or presented retinal vein occlusion (16.1%) or diabetic retinopathy (11%).⁽¹¹⁾

Similar studies were later performed on Asian population from Malaysia,⁽¹⁰⁾ and Japan.⁽⁹⁾ Kawasaki et al reported an ERM prevalence of 7.9% in the Singapore Census population (higher in Malays than in Caucasians from the BMES, 15.8% vs 6.8%). Age, female gender, hyperopia and narrower retinal arteriolar

diameter were associated with higher prevalence of ERM.⁽¹⁰⁾ The results of the Funagata study reported similar results for the Japanese population and for the BMES.⁽⁹⁾

Optical coherence tomography (OCT) seems to have increased the prevalence of ERM by increasing the sensitivity of the diagnostic procedure. A clinical-setting study on patients undergoing cataract surgery reported ERM in the baseline visit in 15.6% of the cases. ERM was detected adherent to the inner limiting membrane (ILM) and nervous fiber layer of the retina by OCT in the initial phases, although funduscopy did not reveal changes in most of the cases.⁽¹⁴⁾ However, the Handan Eye Study (a population-based study of eye disease in rural China) reported ERM were present in 3.4% of participants and was bilateral in 20.3% of the cases on the basis of OCT and retinal photographs.⁽¹⁵⁾

Pathophysiology

Even though most of the cases of ERM are idiopathic^(11,16) they have also been reported to occur in association with different ocular conditions such as retinal vascular diseases (obstructive vasculopathies, diabetic retinopathy and macro aneurysms),⁽¹¹⁾ ocular inflammation (sarcoidosis, pars planitis and almost any posterior uveitis),⁽¹⁷⁻¹⁹⁾ intraocular tumours (hamartomas, angiomas),⁽²⁰⁾ blunt and perforating trauma,⁽²¹⁻²³⁾ surgery (especially laser, cryotherapy and retinal detachment surgery)⁽²⁴⁻²⁶⁾ and retinitis pigmentosa.^(27,28)



Different etiologies of ERM may also show as different patterns in OCT, as has been recently shown by Mori et al. Secondary ERM are more likely to be characterized by focal retinal adhesion than are primary ERM, which tend to be globally adherent.⁽²⁹⁾

The exact composition of the extracellular matrix and the pathogenesis of ERM may be different and dependent upon the etiology of the membrane. The presence of collagens, type I-IV, laminin, and fibronectin have been shown by means of immunofluorescence techniques.⁽³⁰⁾ Glial cells and newly formed collagen may play an important role in ERM and macular hole formation as well as in the healing of the retinal defects. Indeed, pars plana vitrectomy with peeling of an ERM, and/or the ILM may induce direct glial cell proliferation and migration.⁽³¹⁾

The role of posterior vitreous detachment (PVD) in the genesis of ERM is not clear. PVD is observed in 80-95% of the cases of ERM. It has been postulated that ERM may be the result of anomalous PVD with vitreoschisis, leaving the outermost layer of posterior vitreous cortex attached to the macula.⁽³²⁾ The adherent posterior vitreous may play an inhibiting role on the cellular proliferation. The possibility that the traction temporarily exerted by the partially detached posterior hyaloid may stimulate the migration and proliferation of glial cells over the retinal surface has been suggested. It has been considered that remnants of vitreous cortex may remain adhered to the surface of retina once the PVD has been completed giving rise to a cellular proliferation leading to the appearance of the ERM.⁽³³⁾

Multiple pathological studies have been carried out about the composition of ERM. Most of these works agree that the cells forming the ERM have a retinal origin, most probably from the glia. However, the origin of these cells remains controversial.⁽³⁴⁾ More recent works have identified cells from the retinal pigment epithelium (RPE),⁽³⁵⁾ fibroblasts,⁽³⁶⁾ hyalocytes,⁽³⁷⁾ and pericytes.⁽³⁸⁾

Natural History

VA usually stabilizes after ERM formation and only 10% to 25% of patients lose one or two lines of vision when followed for a 2-year period.^(39,40) Most of the ERM usually remain unchanged after an initial period of growth. Occasionally, idiopathic ERM may induce slow and progressive vision loss throughout the years. If the vision goes worse the occurrence of other ocular diseases, such as cataracts or age macular degeneration, should be considered.

PVD is reported in up to 90% of the patients with idiopathic ERM.^(39,41) However, PVD does not seem to be a prerequisite for the appearance of ERM, and VA may be poorer and the risk of cystoid macular oedema be higher in eyes with posterior vitreomacular traction than in eyes with PVD.

ERM have been reported to resolve spontaneously, especially among younger patients in association with PVD.⁽⁴²⁻⁴⁷⁾ This finding is more frequent among eyes with incomplete PVD when the vitreous becomes completely detached, though it may also occur in eyes with previous complete PVD.⁽⁴⁸⁾



ERM may also be associated with RPE defects either as a consequence of the ERM or related to the primary cause of the ERM, such as intraocular inflammation, retinal detachment, trauma or surgery. RPE defects are considered to be related to a poorer visual outcome.

Clinical Findings

Most of the patients do not present symptoms and may have a normal vision. Symptomatic cases may present a variable amount of visual involvement, from mild metamorphopsia in the early stages to a marked decrease of VA in well advanced cases. The onset of symptoms may be slow and hardly noticeable in some patients, yet many are acutely aware of a change in vision. Central diplopia, photopsia and macropsia can appear, as well as blurred vision, distortion, diplopia, and even profound central visual loss.

VA among patients with ERM is 20/70 or better in most of the cases.⁽⁴⁹⁾ and less than 5% have vision worse than 20/200.

The diagnosis of ERM is based on clinical findings (Figures 1 and 2). Bio microscopically it is characterised by an increased brightness on the ILM which does not affect the course of the retinal vessels in the early stages, and is better appreciated by contact bio microscopy. The limits of these cellophane membranes are usually poorly defined. The contraction of the ERM may cause tiny folds on the ILM or the retina following a radial pattern. In more advanced cases it may show a white-

gray membrane distorting the retinal vessels with dilated veins and eventually macular oedema. As in other conditions affecting the vitreo-retinal interface, bio microscopy may not completely show the adherence of the posterior hyaloid to the retina.

The amount of retinal involvement may be better appreciated by fluorescein angiography (FA) which reveals vascular distortion and an increased vascular permeability caused by the traction exerted by the ERM giving rise to a macular oedema (Figure 2). The presence of retinal vascular tortuosity and tethering is useful in assessing the extent of retinal wrinkling caused by the membrane. Foveal ectopia causing diplopia can be appreciated as a distortion of the perifoveal capillary net.

Multiple small round haemorrhages may appear on the inner retina which may be associated with microaneurysms and irregular dilation of the retinal capillaries and cotton wool spots caused by blockade of axoplasmic flow. In these cases stretching of the inner retina seems to play a role in the retinal distortion.⁽⁵⁰⁾

Occasionally, and more frequently following retinal detachment surgery ERM may be opaque and thick creating dense retinal folds which may detach the fovea from the RPE and induce xanthophyll pigment migration, markedly reducing central VA. In other cases contraction of ERM and ILM in the perifoveal area may increase the foveal depression which will appear darker and surrounded by a greyish tissue looking like a macular hole.

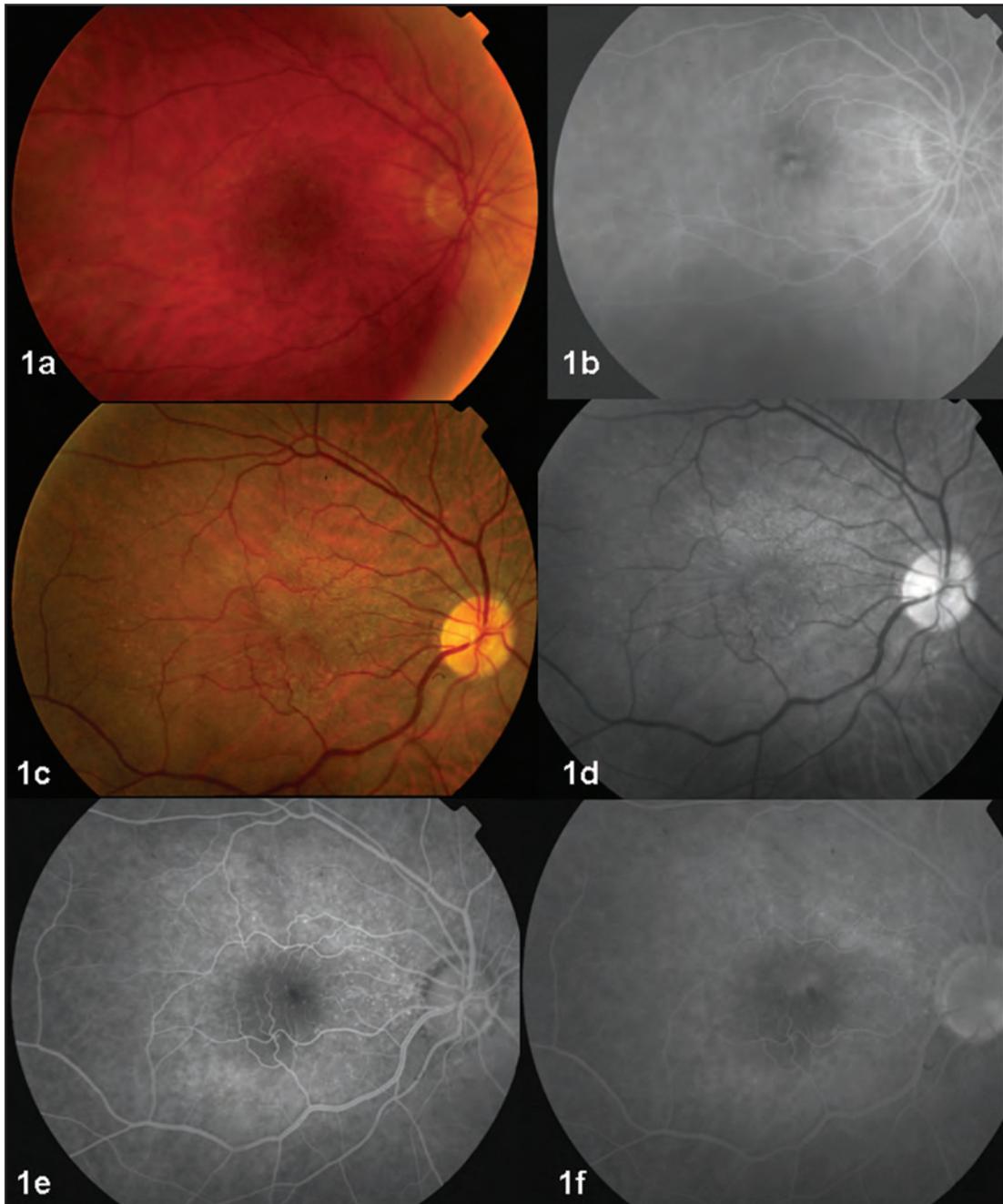


Figure 1: 1a) Retinal photograph (RP) in a case of epiretinal membrane (ERM) showing a thickened macula with increased retinal reflex and a small macular haemorrhage near the fovea. 1b) Fluorescein angiography (FA) shows macular oedema with vascular distortion. 1c) RP showing yellowish ERM with increased macular reflex and vascular distortion that can be better appreciated in the red free photograph. 1d). FA. 1e,1f) shows macular oedema, vascular distortion and pigment migration obscuring the macula.

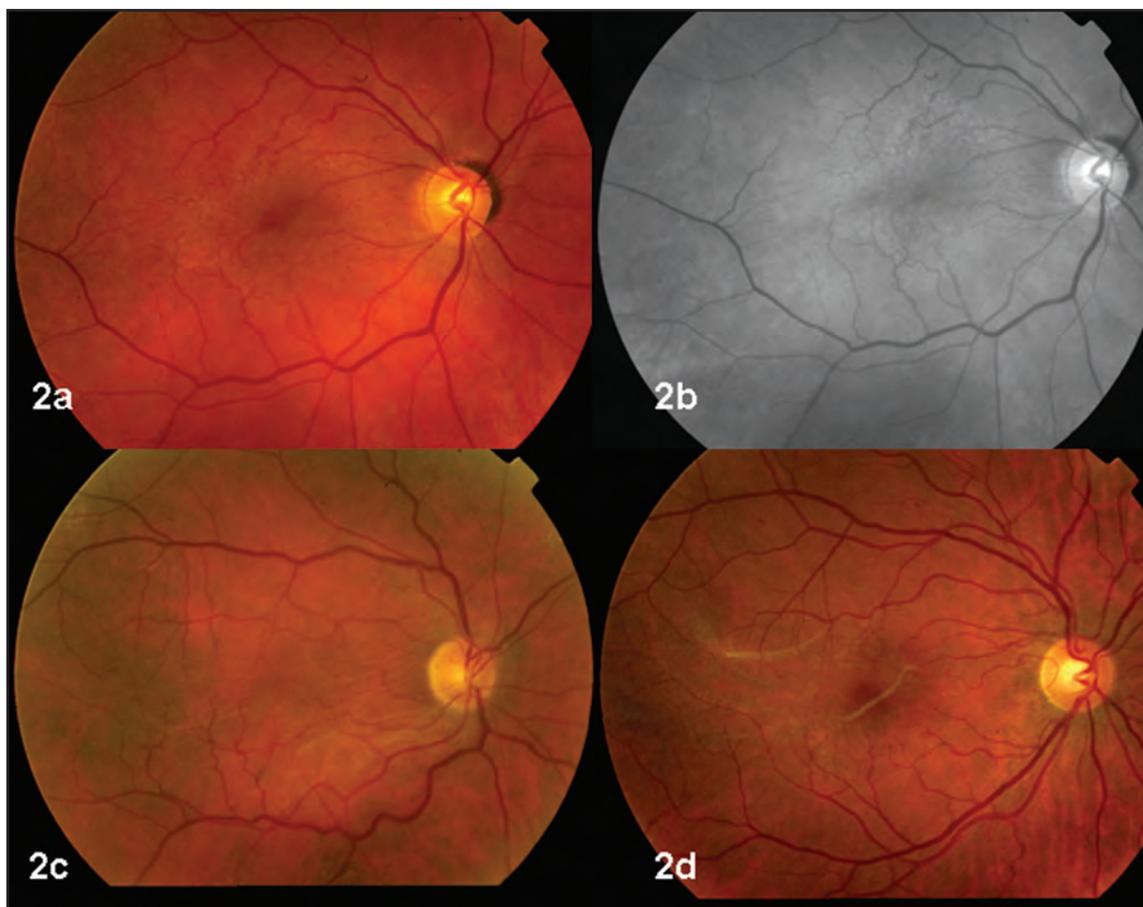


Figure 2: 2a and 2b) RP and red free photograph showing ERM with diffusely increased macular reflex. 2c) ERM showing radial macular folds. 2d) well delimited ERM with foveal detachment showing enlargement of the foveal pigmented area.

B scan may show the presence of macular thickening in those more advanced cases of ERM exerting greater traction on the macula. Perrenaud et al reported identification of ERM and condition of the posterior hyaloid using B scan and compared it with OCT. Preoperative ultrasonography allowed an excellent evaluation of both the peripheral and the posterior vitreous and showed the membrane, permitting visualization of the retinal thickening and the retinal folds. Fol-

lowing surgery, both methods were able to detect membrane remnants. Furthermore, B scan is the only imaging procedure that can be useful when the ocular media are not transparent and allows an excellent global analysis of the anterior and posterior vitreous, which is very useful for the surgeon.⁽⁵¹⁾

OCT is probably the most useful diagnostic tool to identify ERM (Figures 3-5). ERM visualization improves when a flat detachment

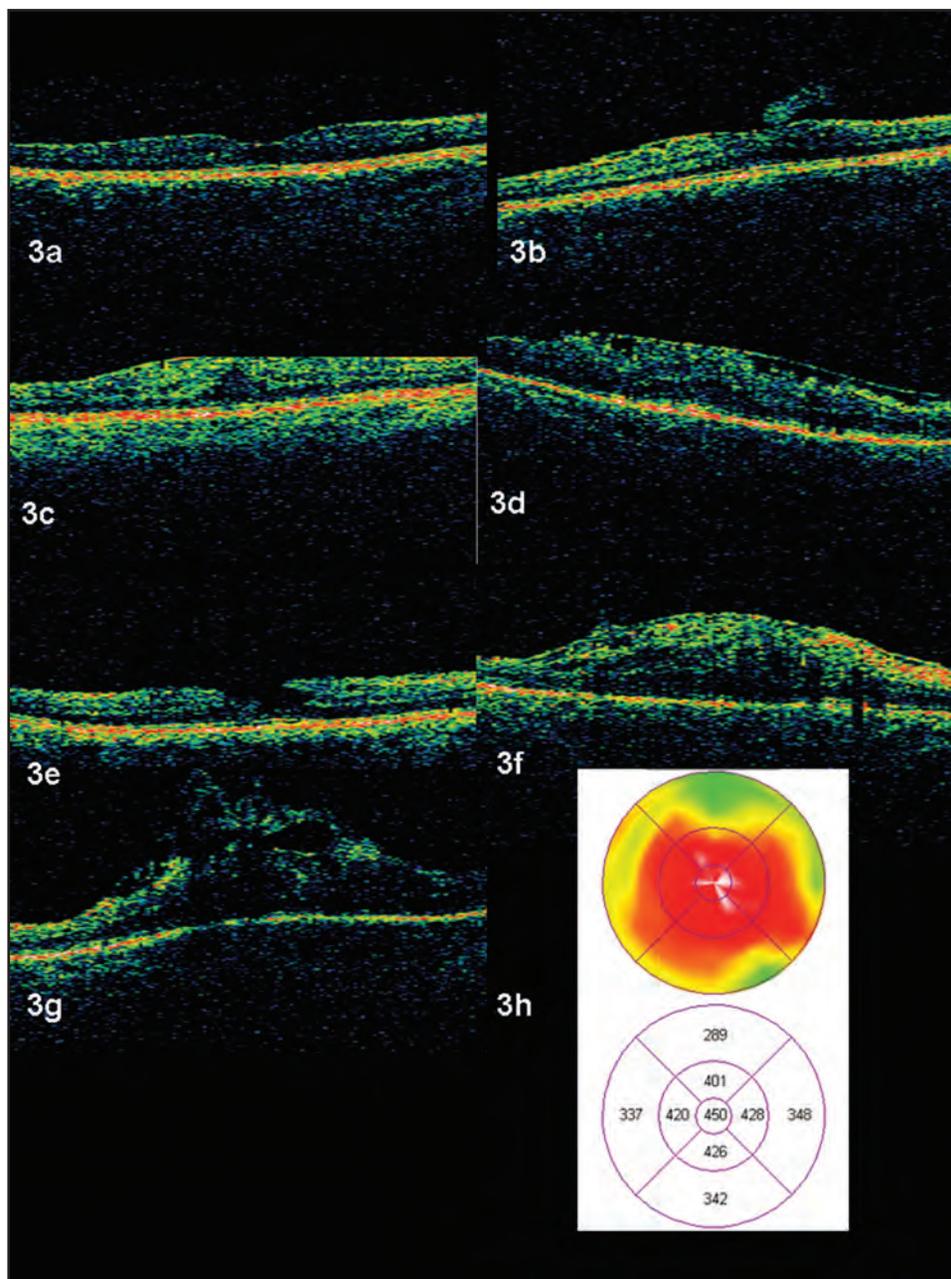


Figure 3: Optical coherence tomography (OCT) in different cases of ERM showing different ERM patterns. 3a) Thin ERM with mild traction causing no macular oedema. 3b) ERM with an adherent tuft to the vitreous. 3c) ERM causing foveal traction with foveal detachment as seen in figure 2d. 3d) ERM with multiple, well delimited adhesion foci to the retina. 3e) ERM causing a pseudo macular hole. 3f) Marked macular oedema in a case of ERM with vitreoretinal traction. 3g) ERM with severe tractional tufts to the vitreous and 3h) colour code graphic of macular oedema.

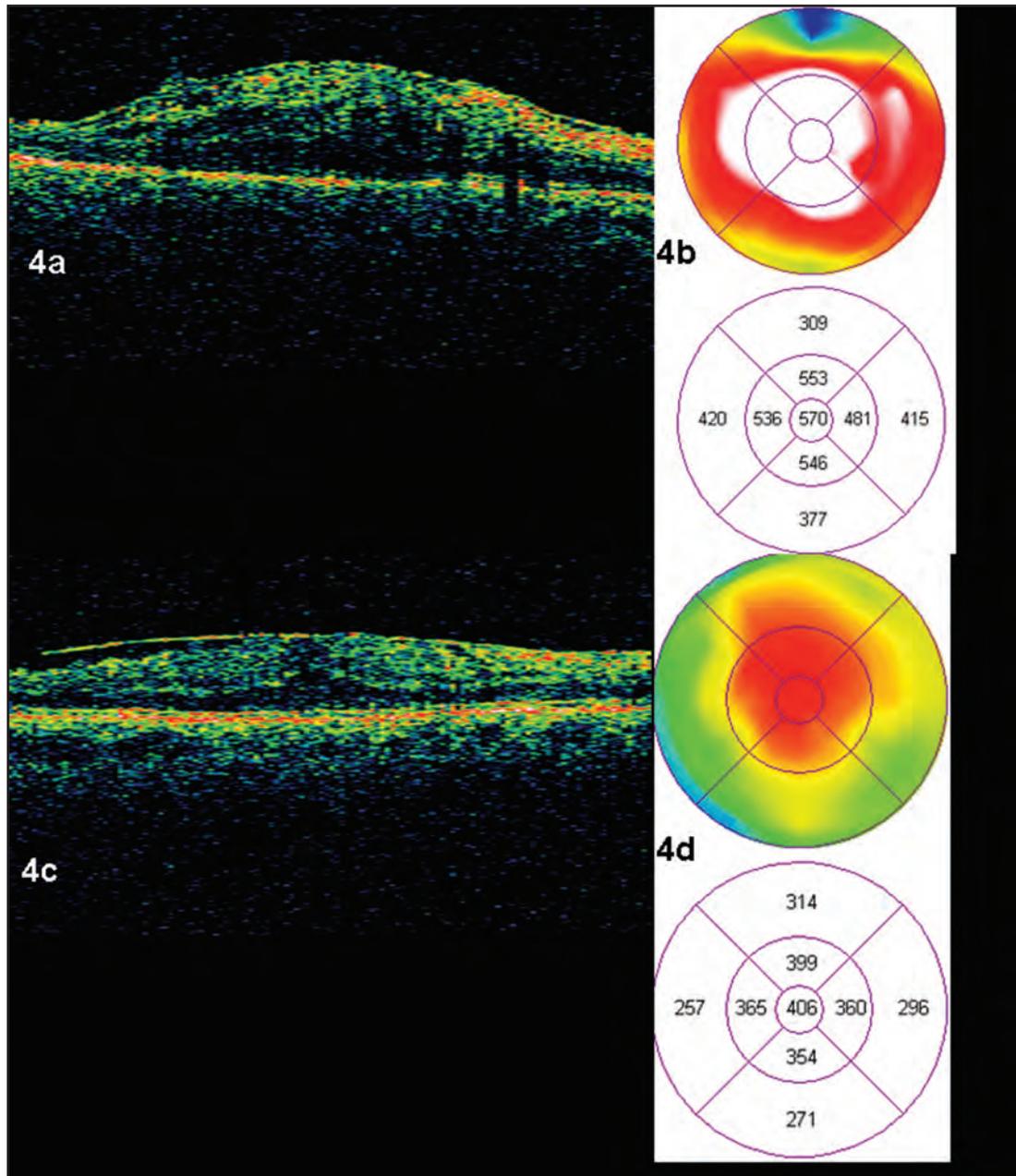
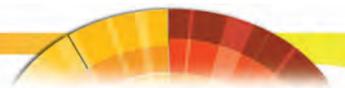


Figure 4: 4a and 4b) OCT in a case of macular traction induced by ERM showing the ERM and colour code graphic. 4c and 4d) A less severe macular edema with foveal detachment.

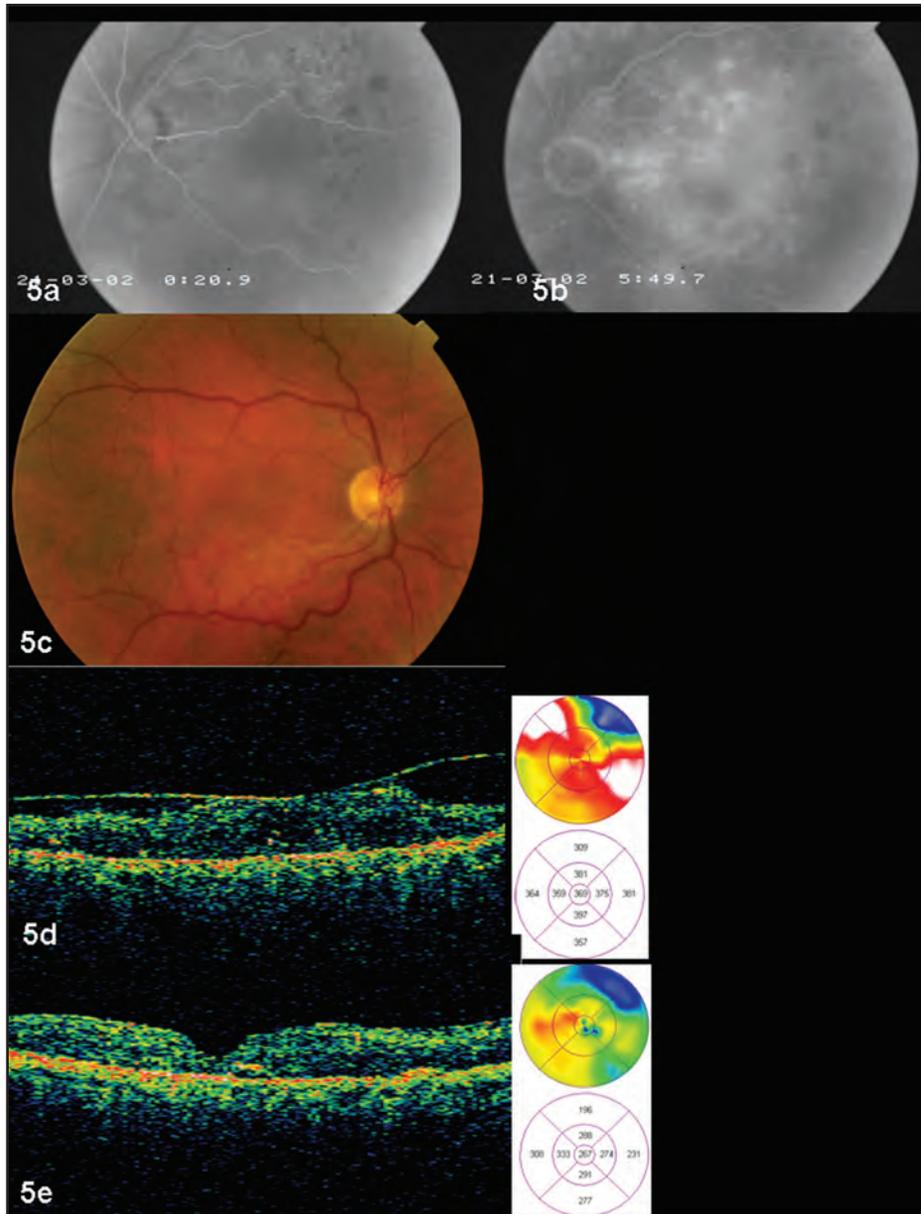


Figure 5: 5a and 5b) FA and (5c) RP in case of diabetic retinopathy with ERM. 5d) shows ERM preoperatively with multiple adherent foci to the retina and macular oedema and 5e) shows the thickened macula after surgery free from the ERM. However, due to the pre-existing condition of diabetic retinopathy visual acuity remained unchanged in 20/400.



from the retinal surface with focal points of attachment is present, which is estimated to occur in up to 30% of the patients.⁽⁵²⁾ According to this series, ERM was undetectable on OCT in 12/186 eyes. Mean central macular thickness measured with OCT correlates well with VA. Quantitative measurements and the assessment of membrane adherence with OCT may be useful in characterizing the surgical prognosis of eyes with ERM.

Posterior hyaloid appears in OCT as a reflective membrane somewhat similar to ERM, though some differences exist:

- ERM is thicker than the posterior hyaloid.
- ERM presents a higher and more homogeneous hyper reflectivity, whereas posterior hyaloid usually shows hyper reflective areas.
- Posterior hyaloid is usually more detached from the retina than the ERM.

Treatment

The aim of vitreoretinal surgery is to remove ERM causing significant vision loss. The indications for surgery may vary individually but it is usually reserved for those cases in which VA has decreased at the level of 20/60.⁽⁵³⁻⁵⁶⁾ Occasionally, patients with VA 20/50 or better may undergo surgery when incapacitating metamorphopsia or monocular

diplopia occur or the patient requires VA improvement to continue working.

The usual procedure for ERM is three-port 20G vitrectomy which is presently being replaced by 25G and 23 G procedures under peribulbar (more rarely, topical) anaesthesia with sedation (Figures 6-7).

Following central core vitrectomy, a posterior hyaloid detachment is induced by aspiration of the posterior hyaloid in the area surrounding the optic disk with an extrusion cannula or the vitrectomy probe. Triamcinolone acetonide has been used to aid in the complete dissection of the posterior hyaloid.⁽⁵⁷⁻⁶⁰⁾

In order to facilitate the visualization and removal of ERM, different vital dyes have been used. There is a consensus that the application of vital dyes facilitates the delicate removal of intraocular membranes during vitreoretinal surgery. Controversy still remains around various issues, mainly concentration and potential toxicity and safety.

Due to its availability, indocyanine green (ICG) was the first dye used. Burk performed ILM stain in cadaveric eyes using a 0.5% ICG solution injected into the posterior vitreous cavity over the macula, allowing the dye to settle for 5 minutes and removing it by mechanical aspiration. Bright green staining of the ILM resulted from this procedure which greatly facilitated ILM peeling by improving direct visualization of the membrane.⁽⁶¹⁾

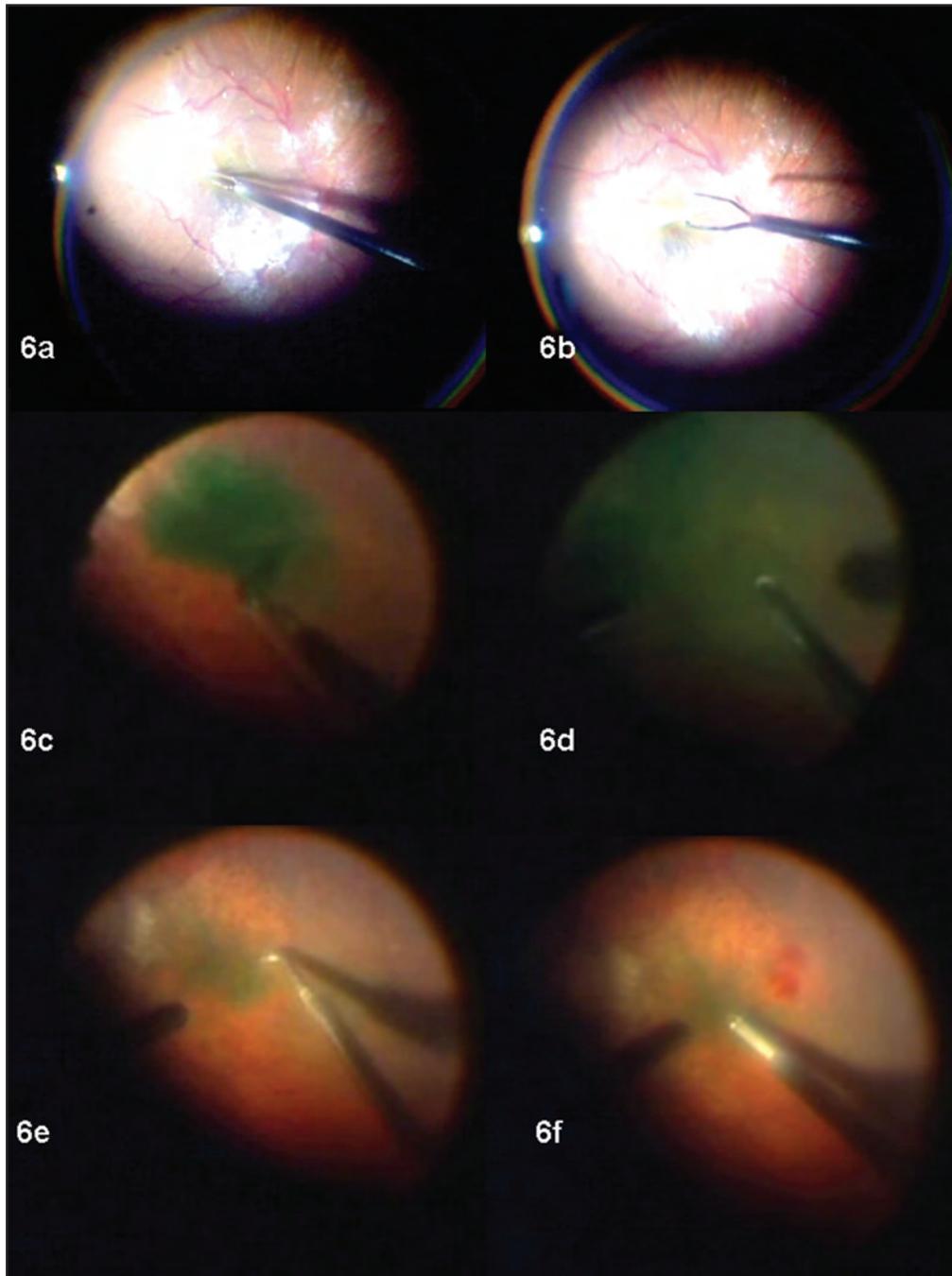


Figure 6: 6a and 6b) Two steps of unaided, direct ERM peeling. 6c) Intraocular injection and 6d) removal of indocyanine green (ICG). 6e) The border of the ERM is lifted with a pick and 6f) dissected with the aid of intraocular forceps. Notice the presence of a small retinal haemorrhage.

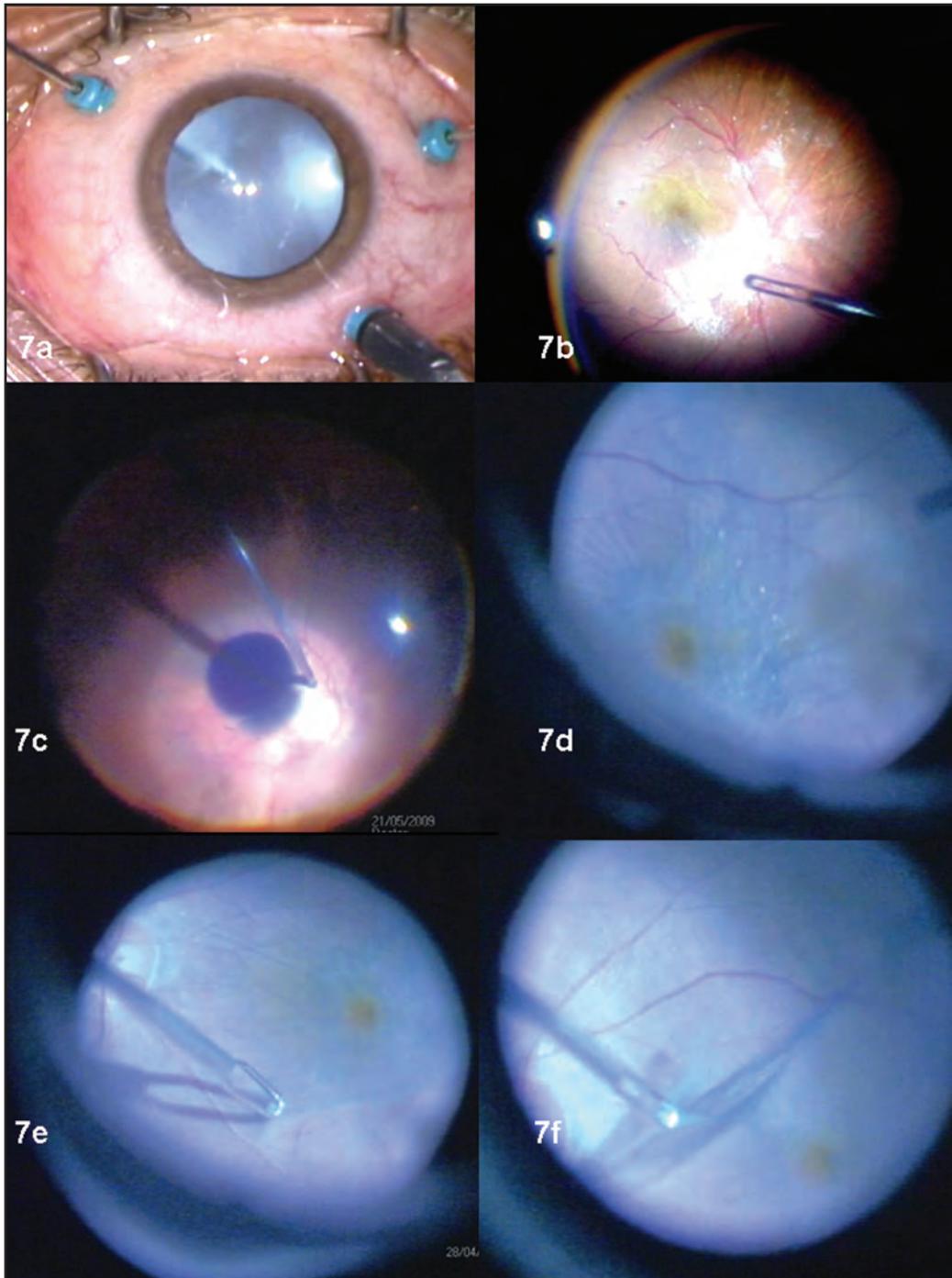
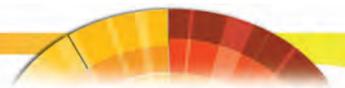


Figure 7: 7a) Central core vitrectomy using 25 G instruments. 7b) Persistence of macular folds following ERM removal. 7c) Trypan blue injection and 7d) aspiration. ERM is stained and its border is grasped 7e) and dissected 7f) until finally removed.



A concentration of 1.25-mg/ml ICG under air stains the macular ILM and ERM consistently well facilitating surgery.⁽⁶²⁾ However, ultra structural findings of the ILM suggest that the cleavage plane may not be exactly at the inner aspect of the ILM but within the innermost retinal layers and that the use of ICG as surgical aid might alter the structure of the retina to some degree.⁽⁶³⁾ In a series reported by Haritoglou et al using commercially available ICG with a concentration of 0.05% and an osmolarity of 275 mOsm, an improvement of vision was noted in 86% of patients without and 55% of patients with ICG-assisted surgery, and 35% of patients after ICG application presented with a deterioration of visual acuity. Large visual field defects were detected in 7 of 20 patients after ICG staining.⁽⁶⁴⁾ However these results are not consistent in other reported series. The results of several studies suggest that ICG toxicity to the retina is dependent on the dye concentration and the osmolarity of the solvent solutions, as well as on the length of dye exposure time and of the vitrectomy endolight illumination. With respect to the safety margins and profile, ICG is therefore a useful surgical tool that is still widely applied, but that may be replaced by more inert and efficient vital dyes.⁽⁶⁵⁻⁶⁷⁾

Trypan blue has also been used at concentrations of 0.15,⁽⁶⁸⁾ to 0.6 mg/ml in 0.1 mL for 1 min under air for ERM staining.⁽⁶⁹⁾ Trypan blue stains both ILM and ERM. However, some toxic effect has been reported following the use of this substance, though it seems to be less toxic than ICG as was demonstrated by Jin et al.⁽⁷⁰⁾ A retrospec-

tive study performed by Perrier et al revealed a median preoperative VA of 20/100 vs a mean postoperative VA of 20/60, and 74% of the patients improving their visual acuity by at least two chart lines. No adverse reaction related to trypan blue was observed up to 1 year postoperatively.⁽⁷¹⁾

Stalmans et al reported on the use of double vital staining in premacular fibrosis to facilitate complete removal of all epiretinal tissue: the epiretinal pucker was removed after staining with trypan blue, whereafter the inner limiting membrane was peeled after staining with infracyanine green.⁽⁷²⁾

Dyes such as Evans blue and light green may stain the internal limiting membrane very well, whereas fast green and indigo carmine may be very safe to the retina. Bromophenol blue and Brilliant Blue G (BBG) may be even better novel agents. During the past three years BBG has entered the group of vital dyes for vitreoretinal surgery.^(73,74) BBG seems to be an alternative vital staining dye with a good biocompatibility. Comparing the effects with ICG or trypan Blue, BBG exhibits a more favourable safety profile.⁽⁷⁵⁾

The dyes currently used for different steps in chromovitrectomy are: triamcinolone acetonide for vitreous identification; ICG, infracyanine green, and BBG for internal limiting membrane identification; and trypan blue for ERM identification.⁽⁷⁶⁾

Our preferred method is to prepare the vital stain solution in cold 5% Dextrose in order to facilitate its deposit on the retina.



Following injection of the dye near the posterior pole, the infusion port is closed in order to prevent turbulences of the intraocular fluid and the intraocular lights are turned off to prevent phototoxicity to the retina.

Two minutes afterwards, the remnants of the dye are aspirated with the vitrectomy probe. The vital stain facilitates the identification of the borders of the ERM, which are lifted with the aid of a pick or a barbed microvitrectomy blade which is used to engage the membrane at its edge and elevate it from the retinal surface. The blade is then used to strip away connections to the retina on that side of the membrane where the dissection was initiated. During this initial manoeuvre, a front of elevated membrane is created, taking care not to fragment the membrane by pulling too hard or too long in any one direction. Once an entire side of the membrane has been elevated, Tano forceps or ILM Grieshaber forceps are used to continue the dissection, again elevating the membrane at multiple sites along the advancing edge of residual adhesion. Afterwards, the ERM is dissected until it becomes completely detached from the macular area. It is preferable to grasp the ERM close to the base in order to keep the dissection under control.

Once this advancing edge is close to the fovea, the membrane is grasped so that the fovea can be observed clearly as the membrane is peeled over and free of all macular connections.

In cases of thick and fibrotic ERM, it may be possible to grasp the membrane directly

with an intraocular foreign body forceps and strip it away from the macular surface (Figure 6). Occasionally, no surgical dye is used since a good surgical cleavage plane may exist facilitating the identification of the border of the ERM.

It is not infrequent that macular folds are seen immediately after the ERM dissection (Figure 7b). Small retinal haemorrhages may occur during membrane dissection (Figure 6f). They can be reduced by increasing intraocular pressure, though it is usually not necessary. Xanthophyl pigment migrated from the fovea to the membrane can be observed while removing the ERM.

The aetiology of ERM influences the final result. The prognosis of ERM caused by retinal detachment is usually worse than idiopathic cases. In a study evaluating the results of the membrane extraction in retinal detachment or retinal tears, the factors associated with a better postoperative VA included the presence of thin ERM and not detached macula during the previous retinal detachment. 60 to 90% of the cases gained two or more lines VA after surgery, and metamorphopsia decreased or disappeared in 75 to 85% of the cases. The lapse for normalization of visual function may vary from days to months. Final VA is frequently interfered by cataract formation.⁽⁷⁷⁾ In a similar report of idiopathic ERM, the factors associated with better postoperative VA included an initial VA of 20/60 or better, short duration of the symptoms of blurred vision, the presence of a thin ERM and the absence of a tractional retinal detachment. Macular folds are reduced following surgery



in 80% of the cases and an almost normal situation is achieved in 30% of the cases. Even though a direct relationship exists between the anatomical and the functional outcome, the latter may be worse in the long standing cases.⁽⁷⁸⁾ It has been suggested that eyes with transparent ERM respond better to the surgery than those with opaque membranes.

The most important prognostic factors are VA, presence of macular oedema and duration of the condition. Cases with worse VA usually show greater improvement though the final visual acuity is poorer than those cases with better initial VA. Cystoid macular oedema shows resolution in only 10% of the cases. Functional outcome is usually poorer in cases with longer duration and better when surgery is performed within the two years since the symptoms started.⁽⁷⁹⁾

Among the complications of surgery, the most frequently reported are cataracts (40 to 80% in patients older than 60 years of age, especially during the first year after surgery), retinal phototoxicity and toxicity induced by the vital stains, retinal tears and detachment, recurrences of ERM and less frequently endophthalmitis.^(76,80-83)

The authors have no economical interests in the devices and procedures described.

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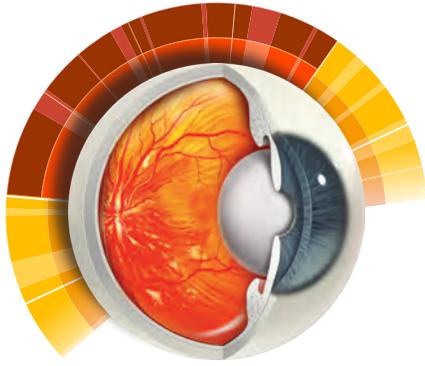
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Fine Needle Aspiration Biopsy in Intraocular Tumors

DAVID E. PELAYES, MD, PHD.,
ANIBAL MARTIN FOLGAR, MD.,
JORGE O. ZARATE, MD. PHD.

Introduction

Classically, the diagnosis of intraocular neoplasias was done through non invasive methods; nevertheless, diverse situations of presentation of intraocular tumors like: previous treatments, systemic implications, unusual clinical presentations or determination of prognosis factors make it necessary to obtain a cytological specimen of the tumor.

Aspirative puncture with a fine needle (FNAB) is a technique that was described and used to obtain cytological specimen from neoplasias, more than 100 years ago. Although it was applied to different tumors, the first report on an aspirative puncture in a solid intraocular tumor was done by

Jakobiec in 1979.⁽¹⁾ At the beginning, it was thought that this technique produced sowing of tumoral cells in the needle tract or it was associated with important intraocular complications. These problems limited its implementation; but nowadays it is known as a safe technique and thus it has been used in more than 200.000 systemic cases with a 25 G diameter or less, without detection of any sowing from the tumor.⁽²⁾

Different authors described its use for cytological diagnosis of intraocular tumors.⁽¹⁻³⁻⁴⁾ Now there are precise indications to carry out this technique.^(5,6) But with the arrival of immunohistochemistry and chromosome studies, the indications to determine important prognosis factors in the evolution of the disease have extended.⁽⁷⁻⁸⁻⁹⁻¹⁰⁻¹¹⁾



Indications

Classical indications to carry out an aspirative puncture are the following:^(5,6)

1. Intraocular tumors that present with differential diagnosis which can not be determined through non invasive methods.
2. Intraocular tumors methastasis suspected in patients where one can not find the primary tumor.
3. Intraocular tumors in immunodepressed patients that have an uncertain diagnosis.
4. Intraocular tumors that require cytological diagnosis confirmation before starting a systemic treatment due to oncological disease, or in order to establish the adequate determination of its stage.
5. In the case the patient requests it before starting a treatment.
6. Determination of prognosis factors (especially the chromosomal ones).

Based on their experience, some authors add another indication like suspicion of growth after treatment of an intraocular melanoma.⁽¹²⁾

Recently, there has been an increase in the use of aspiration puncture with a fine needle previous to the placement of a radioactive plate for braquitherapy in patients

with a clinical diagnosis of posterior uveal melanoma. The goal is to harvest tumor material for histopathological and cytogenetic analysis, i.e. to establish chromosome three monosomy.⁽⁷⁻⁸⁻⁹⁻¹⁰⁻¹¹⁾

Instruments and Surgical Technique

Different factors have to be taken into account when planning the puncture:

- Type of tumor;
- Size and location;
- Associated retinal detachment;
- Clearness of the media;
- Generally, we use retrobulbar or peribulbar anesthesia.

The access to the lesion is linked to the tumor location (Figure 1 a,b). In the case of iridian lesions we have to approximate through the anterior chamber. We make a puncture with a 25g needle in the tangential limbal sector to the lesion with an inclination of 30 to 45 degrees. The approximation has to be slow, avoiding lesions to the structures. The whole procedure has to be done under strict microscopic control.^(5,6,13)

In posterior segment tumors it is important to establish the existence of serous retinal detachment above the lesion, and to locate the tumor before the equator or behind it. A

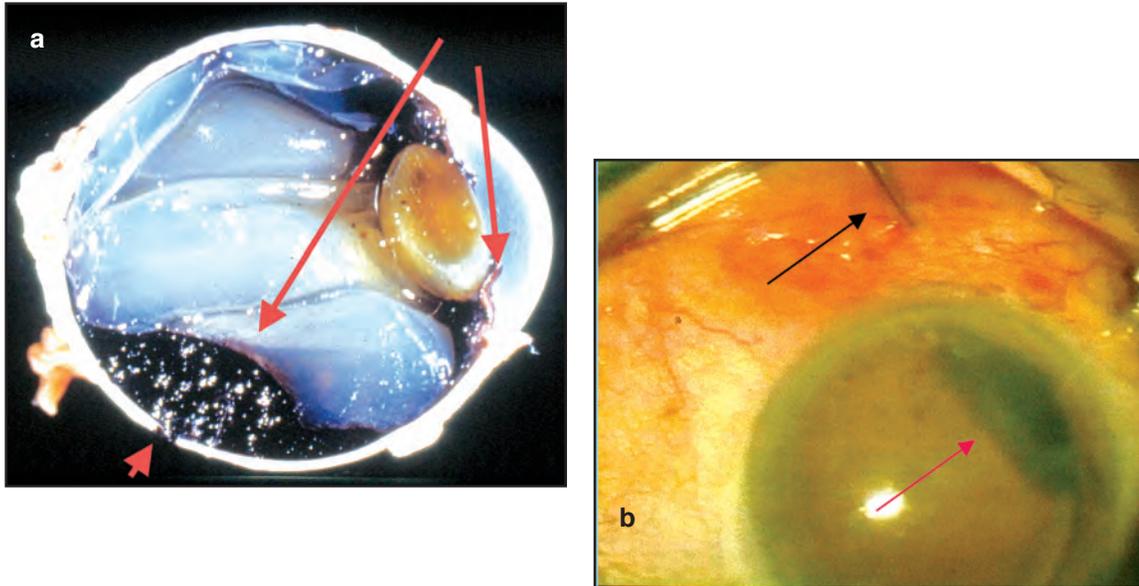


Figure 1: a) Approaches for the aspiration puncture with a fine needle. b) Transcleral direct approach with needle (black arrow). This pictures shows the tumor behind the lens (red arrow).

good maneuver before proceeding with the puncture, is the determination of the size of the tumor with trans - scleral illumination.

If there is no retinal detachment, or scarce sub retinal fluid and the tumor is located posteriorly to the equator, it is convenient to make a transvitreal pars plana approach in a diametrically opposed location to the tumor, having total and constant control through indirect binocular ophthalmoscopy or through surgical microscope and contact magnifying glass. Special care has to be taken when entering the retina, in order no to touch the vessels and to penetrate through the steep

part of the tumor. This procedure is usually done with a 25 gauge needle and a plastic tube connected to a 10 mL syringe, which is then actuated for suction.^(5,8)

If there is a considerable serous retinal detachment over the lesion we have to change the approach. A 3 mm scleral hatch is cut at 80% depth and the tumor is entered directly, also with a 25 gauge needle. The whole procedure is done under indirect binocular ophthalmoscopy.⁽⁵⁾

Another widespread option is the trans scleral approach previous trans-scleral



illumination. With this technique you can use 25 to 30 gauge needles connected through a plastic tube to a 10 mL syringe. Enter the tumor directly. After this maneuver, it is mandatory to place a radioactive braquitherapy plate.⁽⁷⁻⁸⁻⁹⁻¹⁰⁻¹¹⁻¹³⁻¹⁴⁾

There are reports of biopsies with three port vitrectomy approach with gauge 25.⁽¹⁵⁾

Complications

Based on the reports from different authorities we noticed that 54% of the patients that had a puncture in the anterior chamber presented with visible hyperemia that resolved in one week without treatment.⁽⁵⁾

The most frequent complications that arose with transvitreal punctures in the posterior segment were: perforation of the retina (between 27 and 60%) without description of a positive evolution of the retinal detachment.^(5,7)

In 21 to 24% we observed vitreal hemorrhage that resolved spontaneously.^(7,12)

A rare complication was the appearance of a cataract in a patient that presented with diffuse iris melanoma.⁽¹³⁾

It is important to state that there was no tumor recurrence neither in the site of the puncture, nor in the orbital region.⁽⁵⁾

Preparation and Processing of the Specimen

Once you have the material from the puncture with 25 gauge needle, the attainment of cells is 10^6 ⁽¹⁶⁾, and there has to be a preparation in order to be able to make the cytohistopathological exams (Hematoxiline and Eosin (Figure 2), PAS, Mason Tricomic, immunohistochemistry (Figures 3 a, b, c) and chromosome DNA exams.

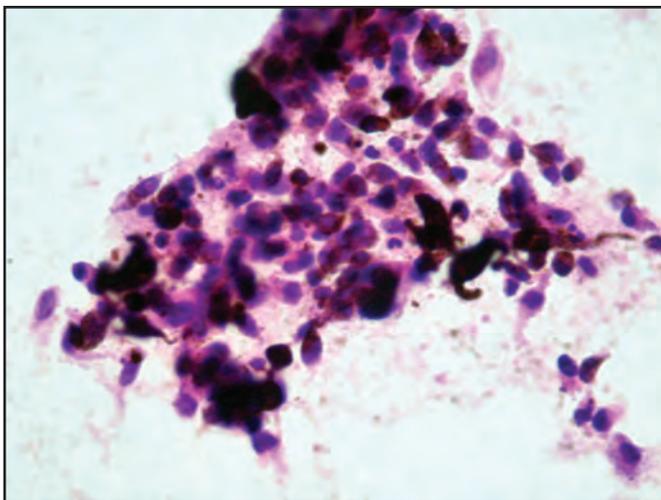


Figure 2: Hematoxiline and Eosin. Sample obtained through aspiration puncture with a small needle.

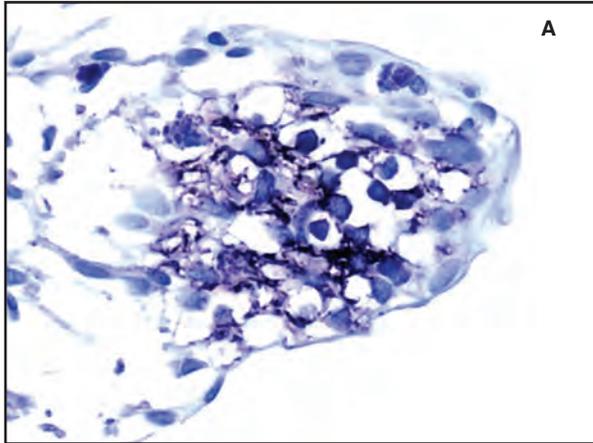


Figure 3 A: Positive HMB 45 immunohistochemistry.

Figure 3 B: Positive MELAN A immunohistochemistry.

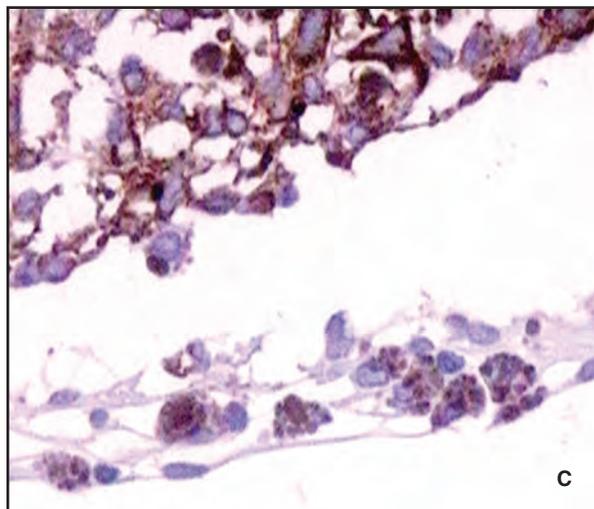
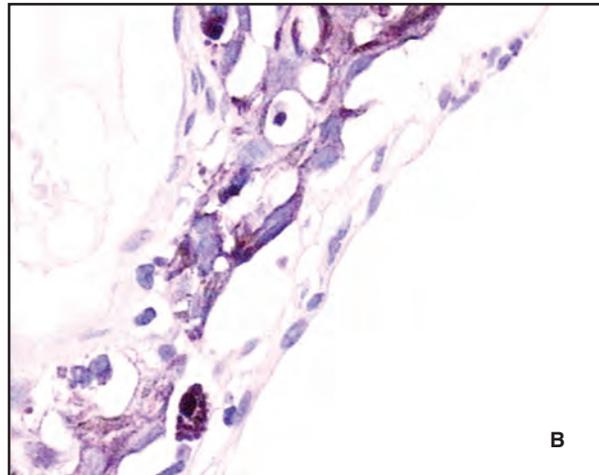


Figure 3 C: Positive Protein S 100 immunohistochemistry.

In coroidal lesions the size is important. Cohen et al.⁽¹²⁾ determined that lesions < 2 mm had a diagnosis efficiency of 40%, while in the case of larger lesions > 4 mm the performance was 90%. Augsburger reported that diagnosis in small coroidal lesions is only 64,7%.⁽¹⁷⁾

Part of the harvested material is spread on a glass plate and fixed with 95% alcohol and air dried. Afterwards routine staining is done and the rest of the material remaining in the aspiration needles is introduced in a balanced HANKS solution (5% acetic acid and alcohol). Later this is processed for cyto diagnosis (PAP-GIEMSA) and for procedures that require special staining (musine and melamine, immunohistochemistry, electronic microscopy,

cytometry and cellular block analysis). The other part of the aspirated material is mixed with phosphate buffer solution and prepared for posterior analysis with techniques for chromosomal determination.^(6,8,9,13,14,15)

The novel preparation technique used in gynecological tumors, is a monolayer technique that allows the grouping of cells in such a way that you obtain a monolayer of cells that simulate a tissue layer (two step cyto concentration, filtering, vortex disintegration, sealing and marking). The sample is put on glasses that form a monolayer of thin smear; due to an electric charge, a circle of 13 mm diameter is formed, with a mean cellular concentration of 60.000 cel./mm² ⁽¹⁸⁾ (Figure 4).



Figure 4: Cellular smears with the AutoCyte technique.



Prognostic Factors

In terms of uveal melanomas, diverse prognostic factors exist which can be obtained through the histopathologic study and the DNA from the tumor, which can be favorable or unfavorable for the clinical evolution of the patient. The most important are:

- Type of cell.
- Cellular proliferation.
- Lymphocyte and macrophage infiltration.
- Chromosome characteristics (chromosome 3 monosomy).

Type of cell: Fusiform A, Fusiform B, Small or big epitheloid, mixed.

Cellular proliferation: The methods to study it include:

1. Miotic Index: very difficult to determine, only cells in mitosis are acceptable.
2. Fluid Cytometry: quantifies DNA and in synthesis.
3. Immunohistochemistry: (MIB-1), ki-67 (anti-proliferative activity).⁽¹⁹⁾

Lymphocyte and macrophage infiltration: Reduction in the patients survival has been associated to a high degree of lymphocitary infiltration in the tumor.⁽²⁰⁾

While infiltration with T lymphocytes is linked to death due to methastasis.⁽²¹⁾

On the other hand, the mortality index raises to the extend of the increase of the macrophage infiltration CD 68+⁽²²⁾ (Figure 5).

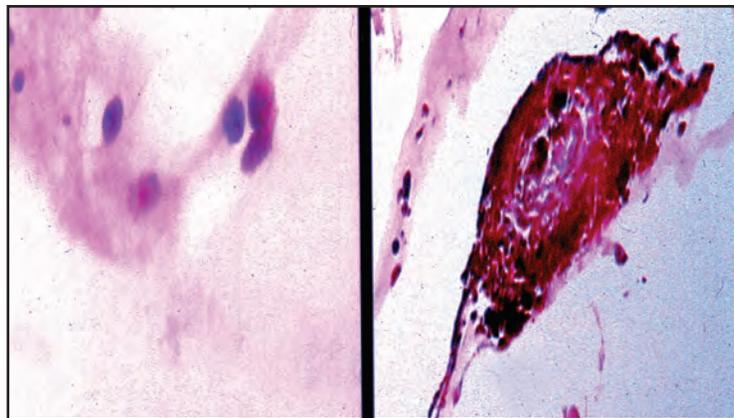


Figure 5: Big macrophage augmentation CD 68+.



Chromosome 3 monosomy: For the genetic assessment of uveal melanomas a FISH (fluorescent in situ hybridization) method is used.

It has been determined that heterogeneity of chromosome 3 monosomy is a frequent phenomenon in this type of tumors.⁽²³⁾ Other studies showed on the follow-up of patients with uveal melanomas and chromosome three monosomy, a 53% metastasis development in a period of up to 3 years.⁽²⁴⁾

In the study where we obtained the specimen through APFV, we needed to know which prognosis factors were distributed homogeneously, because if they were not, then only the positive results were significant and the negative ones were mistaken. The prognosis factors with heterogenic expression are:

- Type of cell (epithelial cell pocket);
- Size of the nucleolus;
- Lymphocitary infiltration;
- Vascular network and neovessels;
- Chromosome 3 monosomy;
- Others.

Conclusions

In certain cases of intraocular tumors the diagnosis cannot be made with conventional methods and it is necessary to harvest a sample of tumor cells. The aspiration puncture

with a thin needle (25 gauge or <) is a safe technique with a relatively low percentage of complications that leads to a definite diagnosis in more than 95% of the cases.

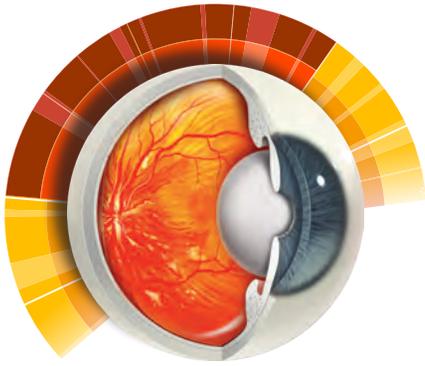
The recent use of FISH for chromosomal characterization of uveal melanomas has increased the indication for this technique as a prognosis and follow-up factor for these patients; but the lack of homogeneity in the distribution of the chromosome has limited its value.

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Management of Intraocular Foreign Bodies

ELENA RODRÍGUEZ-NEILA, MD.,
BORJA CORCÓSTEGUI, MD.

Introduction

Intraocular foreign bodies (IOFBs) are present in a significant percentage of penetrating ocular injuries and may result in severe visual loss. Most of cases are work-related and seen in young, male patients.

The most frequent complications are lens injury, endophthalmitis, retina lesion or detachment and proliferative vitreoretinopathy (PVR).

A focused history and ophthalmic examination are critical to formulate an effective plan. Operative considerations include timing of surgery (delayed versus immediate), primary cataract extraction versus lensectomy, route and instrument used for IOFB extraction, and the role of intraoperative antibiotics.

The aim of this review is providing guidelines for the management of IOFBs.

General Considerations

Traumatic eye injuries with IOFBs may result in severe visual loss depending on the mechanism of injury, size and location of the IOFB, and the occurrence of postoperative endophthalmitis and retinal detachment with PVR.

Clinical diagnosis of endophthalmitis may be difficult in these cases since signs of infection may be masked by the trauma damage.

In a review of ocular trauma from the United States Eye Injury Registry, 25% of patients with IOFB injury had final visual acuities of less than 20/200, despite advances in surgical techniques.

IOFBs are present in a significant percentage of penetrating ocular injuries.⁽¹⁾



The majority of IOFBs are metallic. Other IOFB body matters are concrete, wood and glass. The most common activities at the time of injury are hammering and chiselling.

The entry site is usually corneal and corneoscleral (Figure 1). And the vitreous cavity is the most common final location of the IOFB. A review of the National Eye Trauma System documented the vitreous as the final location in the 47% of IOFB injuries, retina in 33%, pars plana / ciliar body in 5%, lens in 5%, and the anterior chamber (AC) in 10% (Figure 2).

The most common clinical features at the time of presentation are lenticular changes and vitreous haemorrhage. Other presentations as relative afferent pupillary defect, hyphema, uveal prolapse and retinal detachment, are associated with poor visual outcome. Vitreous haemorrhage and poor visual acuity at the time of presentation are also factors predicting poor visual outcome (Figure 3).

The most frequent complications are lens injury, endophthalmitis, retina lesion or detachment and PVR.



Figure 1: Slit lamp photograph. Scleral entrance wound of intraocular foreign body.



Figure 2: Surgery of Penetrating Posterior Segment Injuries and Retained Intraocular Foreign Bodies – Timing of the Surgery. In the penetrating wound site, fibrous proliferations takes the form of thick and rigid fibrotic scars that include the sclera, choroid and retina in one fibrotic mass. This can occur with or without retinal incarceration, resulting in severe traction retinal detachment. (Art from Jaypee - Highlights Medical Publishers).

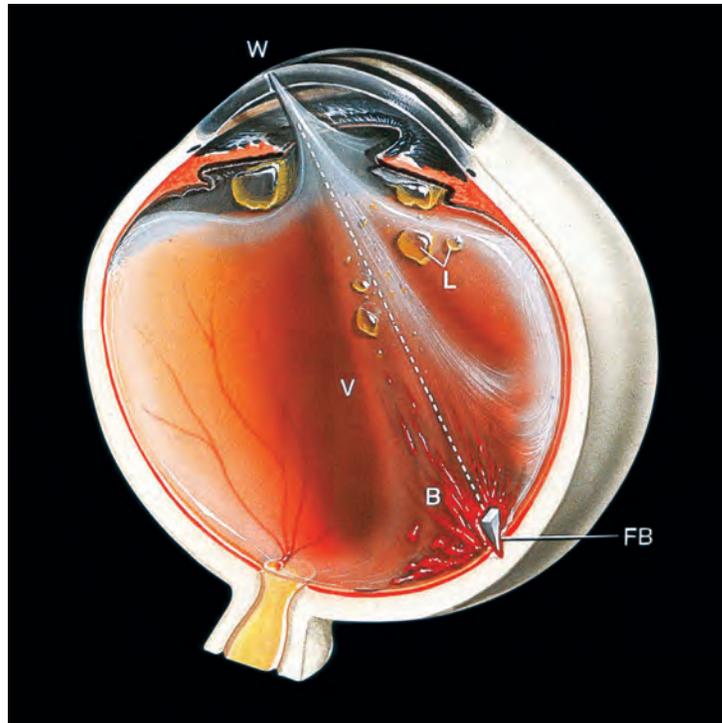


Figure 3: Fundus picture of intraocular foreign body located in retinal surface with consequent vitreous hemorrhage.





Reinterventions are frequently needed. Mean number of operations in most of series is 1.5-2.

Toxicity of metallic IOFBs is more closely related to the active surface area than the volume of the IOFB. Siderosis is caused by the interaction between trivalent iron ions and the proteins in the eye's epithelial cells. Usually, siderosis is developed after some years of ferrous IOFB presence and can be proved by electroretinography (ERG) changes and visual acuity (VA) decrease, that seem to be reversible after IOFB removal.

Chalcosis can start as a rapid, sterile, endophthalmitis-like reaction. Untreated, this violent response may lead to loss of vision within a few hours. After a prompt pars plana vitrectomy (PPV) with IOFB removal, ERG usually improves and good visual acuity can remain.⁽²⁾

The percentage of patients using eye protection is fewer than 10% in most of studies. The importance of protective eyewear should be reinforced to our patients in our office and through workplace safety education programs to prevent ocular injuries.

Preoperative Considerations

A focused history and ophthalmic examination are critical to formulate an effective plan. Also, imaging techniques play an important part in the surgical decision-making to de-

termine IOFB characteristics as shape, size and location. Preoperative systemic antibiotics should be considered.

History and Ophthalmic Examination

Accurate history-taking with attention to the mechanism of injury and material of possible IOFBs should be obtained. Completed ophthalmic exam should be performed with the exception of applanation tonometry when a globe rupture is evident or suspected.

Imaging Techniques

Although a plain X-ray still remains the first line investigation in many units, a negative result should be interpreted with caution if clinical suspicion is high. Plain films may give a false negative result or inaccurately localise the IOFB in up to 30% of eyes.

Computed tomography (CT) of the orbits without contrast is the best choice in suspected or clinically evident globe rupture and can detect IOFB bigger than 0.6 mm³ with a sensitivity of 100%. When an IOFB is found in CT, attention should be paid to its shape, size, location, and material suspected (e.g. metallic, wood, stone, glass, vegetable matter)

Ultrasound, in experienced hands, may identify 93% of IOFB. But the authors only



recommend it, after primary globe closure if there is a globe rupture. Ultrasound biomicroscopy can be used to identify occult IOFBs located in the ciliar body area.

Microbial Spectrum and Preoperative Systemic Antibiotics

The use of preoperative systemic antibiotics should be considered since posttraumatic endophthalmitis is serious complication and a poor visual prognosis factor, particularly in the setting of an IOFB.

Gram-positive organisms as coagulase-negative staphylococci (especially *Staphylococcus epidermidis*) and streptococci species are usually isolate in patients who develop posttraumatic endophthalmitis. But Gram-negative and fungal organisms may also be found. In some cases, polymicrobial infections have been described.

Some organisms that are considered specially virulent, as *Bacillus*, *Pseudomonas*, *Enterococcus* and *Moraxella*, are associated with poor visual acuity outcome.

The third-generation fluorquinolone levofloxacin, can be administered orally (400mg on the evening before surgery and 400mg 3 hours before surgery) and reaches aqueous and vitreous concentration enough to achieve the minimum inhibitory concentration to stop the growth of 90% of major ocular trauma pathogens.⁽³⁾

Surgical Management

If there is an IOFB associated with an acute globe rupture, the scleral, limbal, or corneal laceration should be initially repaired before the start of the vitrectomy.

Operative considerations include timing of surgery (delayed versus immediate), primary cataract extraction versus lensectomy, route and instrument used for IOFB extraction, and the role of intraoperative antibiotics.

Timing of Surgery

Early vitrectomy is advocated when the risk of endophthalmitis is high. This risk increases from 3.5% to 13.4% if removal of IOFB is deferred for more than 24 hours.

Associated retinal detachment also expedites surgical intervention. Other advantages to immediate IOFB removal may include a decrease in the rate of proliferative vitreoretinopathy (PVR), and a single surgical procedure.

But delayed surgical intervention has some pros, as the resolution of anterior segment pathology (e.g. corneal edema), removing the posterior hyaloid in these young patients may be easier, and the inflammation and risk of intraoperative haemorrhage are lower.

When significant choroidal haemorrhage is present, surgery is generally delayed until



the haemorrhage is liquefied (14 days). Unless “kissing sign” (contact between retinal surfaces of choroidal detachment) is present. Then, prompt surgery would be required.

Cataract Extraction versus Lensectomy

In several retrospective case series, cataract extraction and intraocular lens (IOL) implantation at the time of IOFB removal and vitrectomy, appeared to be a safe procedure. But the adequacy of capsular bag and zonular support for a posterior chamber or sulcus IOL should be considered prior to primary IOL implantation. Pars plana lensectomy may be required in traumatic cataract with lens capsule violation or poor zonular integrity.

Pars Plana Vitrectomy (PPV) and Removal of Intraocular Foreign Body (IOFB)

PPV should be performed at the time of IOFB removal of posterior located IOFBs.

Before vitrectomy era, external magnets were used to remove ferrous IOFBs. One study comparing PPV versus external magnet, found that anatomic and functional outcomes were significantly better in patients undergoing PPV.

Complications of external electromagnet were frequent, serious and were not observed

in the PPV group. Modern vitrectomy techniques and the use of intraocular forceps and intraocular magnets have improved the surgical management of the removal of ferromagnetic materials (Figure 4).

Standard 20-gauge vitrectomy offers reliability and versatility when treating the vitreoretinal complications of ocular trauma. The authors do not recommend small-gauge in most cases of ocular trauma. But if small-gauge vitrectomy is performed, two-steps trocar placement is preferable to avoid excessive globe manipulation and elevation of intraocular pressure (IOP).^(4,5)

A 6-mm infusion may be helpful, especially if a choroidal haemorrhage is present. After removing cortical vitreous, posterior vitreous detachment (PVD) may be created if necessary. Then, the vitreous adhesions surrounding the IOFB may be cut circumferentially to ensure that the IOFB is not attached to any structure.

Vitreous removal and posterior hyaloid separation are advocated to limit the fibrovascular proliferation within the tract of perforation and the adhesion of vitreous in the posterior exit wound in order to reduce the incidence of proliferative vitreoretinopathy (PVR) and to improve functional and anatomic outcomes. PVR is usually developed 3 months after the injury but it may occur at any point from 2 to 12 months of injury. Preretinal PVR and subretinal bands may appear. Cases with anterior loop PVR may develop hypotony.



Figure 4: Foreign Body Removal Through Pars Plana Vitrectomy. Next, the foreign body (FB) is grasped with the Sutherland intravitreal forceps (F-made by Greishaber) and removed (from A to B) from the eye through the sclerotomy. Endoilluminator (L). Infusion terminal (I). (Art from Jaypee - Highlights Medical Publishers).

If the cornea is clear enough to perform PPV with wide-angle viewing systems, the authors prefer not to associate keratoplasty since the corneal graft failure is higher at the time of IOFB removal.

The use of the high brightness xenon light source is helpful in IOFB visualization, especially in cases of corneal pathology. Its use with chandelier light source also allows for bimanual manipulation to remove the IOFB and to perform unassisted scleral depression.

Very small IOFBs may be removed with the intraocular magnet or with the conventional membranes forceps. Small and medium-sized IOFBs may be removed with IOFB forceps through the pars plana at the site of sclerotomy with enlargement of the wound if needed, or in aphakic eyes, through a limbal incision. If the IOFB is bigger than 4x4x4 mm, a scleral tunnel may be required (Figure 5).

After IOFB removal, 360° peripheral retina examination with scleral depression is critical to identify retinal tears, retinal detachment

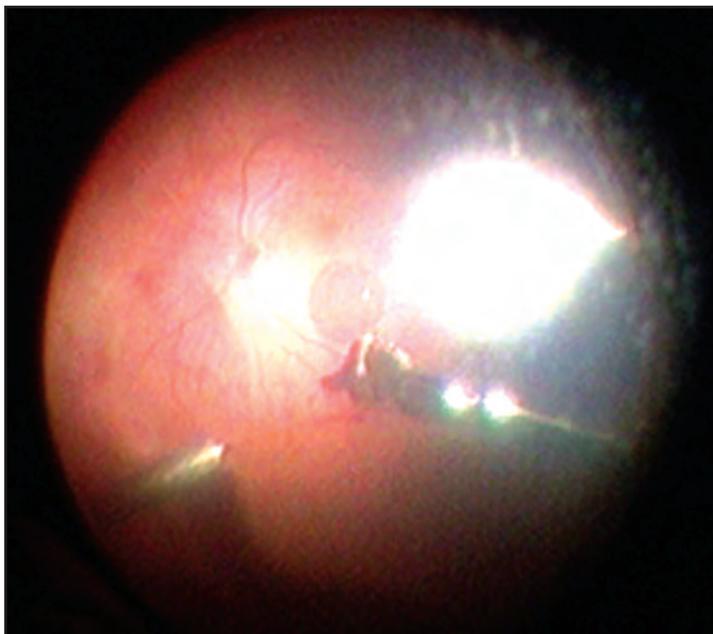


Figure 5: Intraocular foreign body extraction assisted with endomagnet and membranes peeling forceps.

and choroidal detachment. Also, other IOFBs that may be occult in some cases could be identified by scleral depression.

Retinal tears may be treated by endolaser and tamponade. Perfluorocarbons are used if retinal detachment is present. Few studies recommend prophylactic scleral buckle in posterior segment located IOFB cases. In large and anterior located IOFBs, it may decrease the risk of RD.

Series did not find differences in the visual outcome of patients undergoing silicone oil versus C3F8 after vitrectomy. But, usually silicone oil is used in severely injured eyes. A retrospective 23-case series described the use of primary silicone oil tamponade following IOFB removal in eyes with severe concomitant posterior segment injuries, including lacerations of the sclera, choroid and retina. PVR occurred in 70% of eyes and mostly required surgical revision.^(6,7)



Prognosis Factors

Reports in the literature differ in the examination factors associated with poor anatomic or functional outcomes.

Ocular trauma clinical features at the time of presentation that may be predictive of long-term VA include presenting VA, the presence or absence of endophthalmitis, globe rupture, perforating injury, retinal detachment and an afferent pupillary defect.

In the multivariate analysis of most of studies, when an IOFB is clinically observed, the factors associated with poor visual outcomes are corneoscleral entrance wound, uveal prolapse and retinal detachment.

The use of an external magnet is associated with poor visual outcome.

In most of studies, the best predictor of functional and anatomical outcome was the pattern of entrance and exit wounds. If those entering and exiting are anterior to the equator, visual and anatomic outcomes may be better than those with posterior exit wounds. This finding can be explained by the development of vitreoretinal traction at the posterior exit site and the degree of macular injury in posterior globe exit wounds. The amount of macula-involved retinal detachments, choroidal haemorrhage and conmotio retinae involving

the macula is significantly less with anterior exit wounds.^(8,9)

Conclusions

Penetrating ocular injuries with IOFB associated, continues to be a major cause of visual impairment.

Initial evaluation includes a complete history, ophthalmic exam and imaging techniques to identify IOFB location and characteristics. Controversies exist regarding immediate versus delayed IOFB removal. Multiple factors should be considered prior to decide the surgical timing and plan. Above all, the presence of endophthalmitis and retinal detachment, require prompt surgery.

Recent studies have demonstrated that the administration of systemic and topical antibiotics pre and postoperatively may decrease the incidence of endophthalmitis.

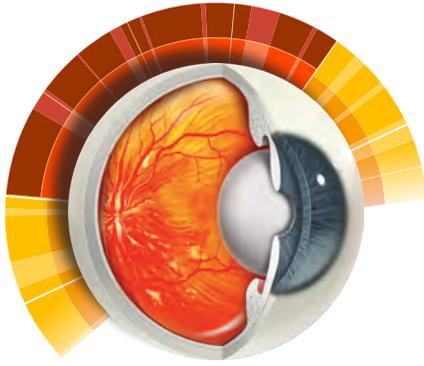
Frequent postoperatively visits are required to detect and treat endophthalmitis, retinal detachment and PVR, which are associated with poor visual outcomes.

Patient education, occupational safety, and advancement in microsurgical techniques continue to help improve visual and anatomical outcomes.⁽¹⁰⁾



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Endophthalmitis

MANISH NAGPAL, MD.,
ANIL PATIL, MD.

Endophthalmitis is a rare catastrophic complication, potentially the most devastating, of intraocular surgery or trauma. It involves inflammation of intraocular tissues, usually caused by an infection. Sterile non-infectious endophthalmitis may be a result of retained lens material and toxic agents. Panophthalmitis is an inflammation of all coats of the eye including intraocular structures. It is presented here because the management of endophthalmitis may require a vitrectomy and can be associated with many vitreo-retinal complications.

Exogenous endophthalmitis is more commonly seen following cataract surgery, penetrating injuries of the globe and infected glaucoma filtering blebs. Endogenous infection occurs in the setting of intravenous drug abuse and systemic immune suppression or incompetence.

Although the rate of postoperative infection is considerably lower in ophthalmic surgery than in other types of surgery, the severe consequences of postoperative endophthalmitis make it essential for every ophthalmologist

to understand its diagnosis, management, and prophylaxis.

Prevention

Preoperative Evaluation and Recognition of Risk Factors

Intraocular infection is preventable to a great degree. It is interesting that once the importance of sterility was recognized, the incidence of endophthalmitis actually fell in the West, long before the introduction of antibiotics. With the elimination of other risk factors, the rate has gradually dropped a little further in recent years. Antibiotics can be effective for the treatment of established infections. In preventing endophthalmitis, however, it is an understanding of the perioperative risk factors that is important. The most critical are pre-existing infectious processes around the eye, lids, adnexa, lacrimal system and in the upper respiratory tract that might contribute organisms to the surgical field. The lacrimal system should be patent and functional so that fluids do not stagnate.



Routine irrigation is not recommended unless there is evidence of obstruction such as tearing, discharge or reflux. Palpation of the lacrimal sac for reflux is appropriate.

There is very strong evidence that in the overwhelming percentage of endophthalmitis cases, the offending organism actually comes from the patient. While there have been epidemics of infection caused by contaminated irrigating solutions and lenses, most cases of surgical endophthalmitis are caused from organisms indigenous to and colonized in the adjacent face and eyelids such as *Staphylococcus epidermidis*, or *Propionibacterium acnes*. Preventing these organisms from contaminating the surgical field is the goal of prophylaxis.

The use of dilute antibiotics in the irrigating fluid during cataract surgery is contentious. Use of aminoglycosides such as gentamicin in the irrigating solution may be inappropriate, since gram-positive organisms which are seen most commonly as the cause of endophthalmitis are poorly treated by these antibiotics. Similarly, the use of vancomycin with any irrigating solution may not make theoretic sense due to the fact that although vancomycin is effective against gram-positive organisms, this medication needs several hours in contact with the bacteria to kill them and may not remain in the anterior chamber for more than one to two hours following surgery. There is also the theoretic risk of antibiotic resistance increasing by the widespread use of antibiotics within the irrigating solution.

Preparation for Surgery

Whether preoperative antibiotics should be administered to every patient is still

controversial. It is not our practice to use antibiotics prophylactically prior to surgery, and we have experienced extremely low incidences of postoperative endophthalmitis. Although one study suggests that antibiotic drops administered four times a day prior to surgery virtually sterilizes the conjunctiva, there is little evidence that this actually makes a difference in the infection rate provided that other preventive steps are taken.

Use of a specific method for preparing the skin and draping the eye can virtually eliminate all organisms from the surgical field and dramatically reduce the rate of endophthalmitis. Preoperative installation of 5% povidone-iodine solution has been shown to be highly effective in eliminating organisms in the conjunctival sac. This leaves the conjunctival sac sterile. It is important to use the solution of povidone-iodine rather than the detergent which is highly toxic to the cornea. Povidone-iodine is also painted on the surface of the eyelids, the brow, the face, and the adjacent part of the nose. Next, a cotton-tipped stick dipped in the solution is used to paint the lid margins. The solution is allowed to dry. The tissues are gently coated without excess pressure on the lids.

Pushing or squeezing the lids margins can express organisms from deep in the glands onto the conjunctiva and lid surface. Next in importance after preoperative preparation is prevention of contamination by organisms that can be expressed from the lids and glands. This can be achieved by proper draping. The principle is to cover the lid margins and skin in a way that prevents entry of organisms into the conjunctival sac. Steri-strips or brow tape can be used along the lid margin to access the lashes and stick them back against the eyelid. Trimming the eyelashes is controver-



sial-while lash trimming can reduce bacterial load in patients with significant blepharitis, it may stir up organisms at the roots of the lashes. As the patient is being draped, the nurse or the assistant can hold the lids apart with two cotton-tipped sticks so that the drape goes directly over the cornea. The surgeon then incises down the middle of the drape. A retractor or speculum can be used to tuck the plastic drape underneath the lid into the fornix. This procedure results in a sterile field. To reiterate, careful skin preparation is the most important step for preventing infection.

European Society of Cataract & Refractive Surgeons (ESCRS) multicenter study of the prophylaxis of endophthalmitis after cataract surgery suggested that intracameral cefuroxime (1 mg in 0.1 mL normal saline) administered at the time of surgery significantly reduced the risk for developing endophthalmitis after cataract surgery. The incidence rate observed in those treatment groups not receiving cefuroxime prophylaxis was almost 5 times as high as that in the groups receiving this treatment. Intracameral vancomycin has been used intracameral quite routinely by a lot of surgeons. Recently moxifloxacin is being advocated for the same usage. The preparation of Vigamox for intracameral use is simple.

A new bottle of Vigamox is opened in the OR. A 10-mL syringe with a 20-gauge needle is used to draw 2 mL of Vigamox into the syringe. The same needle is then inserted into a new 25-mL bottle of BSS, and 8 mL BSS is drawn up into the syringe. This combination yields a 5:1 dilution of the original 500 $\mu\text{g}/\text{mL}$ Vigamox to 100 $\mu\text{g}/\text{mL}$. Rolling the syringe promotes mixing of the solution, which is already well combined by

the turbulence of drawing the BSS up into the syringe after the Vigamox.

A 0.5-mL aliquot of the Vigamox mixture is injected from the same syringe, without changing the needle, into a small medicine cup on each case's scrub table just before it is needed. Next, the scrub nurse draws the solution into a TB syringe. She then attaches a 27-gauge hockey stick cannula to expel any air and all but 0.2 mL of the Vigamox solution. She hands the syringe to me, and I inject 0.1 mL of the Vigamox into the eye through the side port incision, across the anterior chamber, and under the capsulorhexis' edge. This process bathes the IOL in moxifloxacin, achieving antibacterial prophylaxis and pressurizing the anterior chamber simultaneously, and it is the final step of the procedure. A 0.2-mL Vigamox solution is given to the surgeon, rather than only 0.1 mL, because the extra amount allows the surgeon to expel any air from the cannula before inserting it into the eye.

Acute Postoperative Endophthalmitis

Postoperative endophthalmitis can be classified by the interval in time after surgery when the infection manifests. Acute infection occurs within a few weeks of intraocular segment surgery, most typically between 2 and 7 days. The most common pathogens implicated in acute endophthalmitis today are *Staphylococcus epidermidis* and coagulase-negative staphylococci. In past years the predominant pathogens were more virulent organisms such as *Staphylococcus aureus*, streptococci, and Gram-negative bacteria, which fulminate in the first 24 - 48 hours after surgery.



Acute postoperative endophthalmitis usually manifests as a sudden loss of vision accompanied by pain. However, the ophthalmologist should not be lulled into complacency by the absence of pain. Similarly, the eye may appear relatively quiet externally. The presence of a hypopyon, diminution or absence of the red fundus reflex, or the formation of a pupillary membrane are other important indicators of postoperative infection.

Chronic Postoperative Endophthalmitis

Thanks to the work of Meisler and others, we know that persistent, low-grade postoperative inflammation is usually infectious in origin and that low-virulence infections can persist in the eye for months or even years. Delayed or chronic postoperative endophthalmitis can present several months to more than one year after surgery.

Chronic postoperative endophthalmitis presents quite differently than acute endophthalmitis. It is usually not heralded by a significant initial decrease in vision, but remains indolent and is often detected only upon careful examination. Inflammation in the anterior chamber that responds to topical steroids and reappears when steroids are tapered off should alert the ophthalmologist to examine closely the intraocular lens, the haptics, and the capsular bag. Any white accumulations or plaques should be identified as infectious organisms. Other signs of chronic postoperative endophthalmitis include keratic precipitates, vitreous reaction, or beaded fibrin strands in the anterior chamber.

The organisms that produce chronic, late-onset endophthalmitis tend to be of low virulence. *Propionibacterium acne* is commonly implicated; however, infections by yeasts such as *Candida albicans* or *Candida parapsilosis*, and other pathogens of lower virulence have been reported.

Although these organisms grow slowly and are not very effective in overcoming the immunologic defenses of the eye, they can be sequestered within the capsular bag out of reach of host defenses and thus resistant to elimination. However, they do incite a persistent inflammatory reaction. The interval to presentation and the severity of symptoms usually correlate directly with the virulence of the organism.

Sterile Endophthalmitis

Severe marked intraocular inflammation following cataract surgery may closely mimic an infection. It presents mostly early on in the postoperative period, but can occur even after several months of the surgery. History of previous intraocular inflammation, pseudoexfoliation syndrome, inadequate mydriasis at the beginning of surgery, difficult intraoperative course, problems with IOL implantation, mechanical irritation of the iris with the intraocular lens, retention of lens fragments, residual monomers on PMMA lenses, topical anesthetic agents entering the eye, etc. are considered important risk factors for developing an enhanced postoperative inflammatory response.



Hypopyon may be seen as the initial manifestation in such cases. Fibrin, a strong indicator of infection is usually mild or absent in sterile endophthalmitis. It manifests very early on in the postoperative course, usually within the first 24 to 36 hours. On the whole, the clinical picture is much less severe, with mild diminution of the fundal glow, mild vitreous haze, absence of focal infiltrates or nidus of infection. Use of ultrasound can describe and pin-point an inflammatory process affecting only the anterior segment of the eye versus a vitreous reaction, increasing vitreous opacities, or retinal or choroidal detachment or thickening.

The increasing popularity of triamcinolone injections for many disease entities associated with macular edema has led to recent reports of the complications associated with this treatment. Intraocular pressure elevation and endophthalmitis are recognized complications of Intravitreal triamcinolone injections. Although some patients appear to have an infectious endophthalmitis, many of the reports detail a “presumed noninfectious endophthalmitis” or “pseudoendophthalmitis” that resolves without invasive treatment that necessitate proper

informed consent from patients undergoing this procedure.

However, it is of utmost importance that all unexpected postoperative reactions of the eye should be considered as infective, unless proven otherwise.

Diagnosis

The ophthalmologist must maintain a high index of suspicion for endophthalmitis in patients with persistent or increasing intraocular inflammation above the expected level because definitive management of postoperative endophthalmitis begins with the correct diagnosis, and early treatment is critical in achieving a good outcome. Although clinical findings may be highly suggestive, the diagnosis should be secured and antibiotic therapy guided by anterior chamber and vitreous taps for culture (Figures 1 and 2). An anterior tap by itself is not sufficient because in up to 40% of cases in which the vitreous tap is positive, the anterior chamber tap is negative. The vitreous tap should be obtained before antibiotics are administered.

Figure 1: Technique of Diagnosis with Aqueous Tap. A 27 or 26 gauge needle is inserted into the anterior chamber by the limbus to obtain 0.1 – 0.2 ml of aqueous tap (B). Intraocular lens (IOL). (Art from Jaypee Highlights Medical Publishers.)

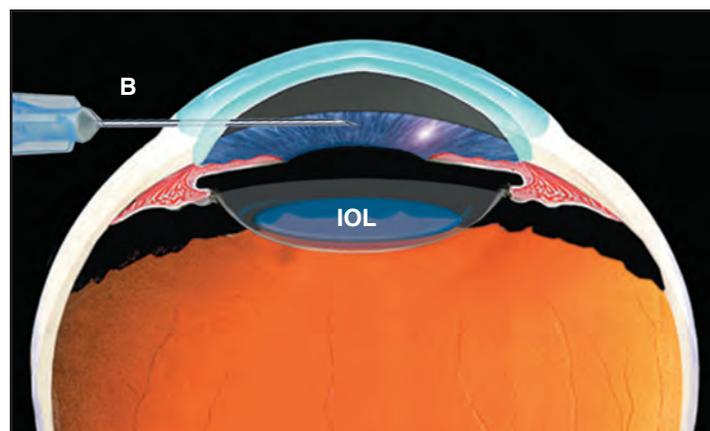
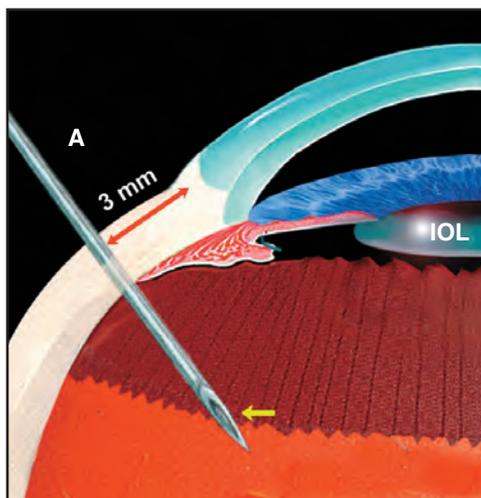




Figure 2: Technique for Vitreous Tap in Diagnosis and Intravitreal Administration of Antibiotics. A 23 gauge needle is inserted through the sclera at 2 – 3 mm from the limbus (A). The needle is used to remove a sample of vitreous or to inject the antibiotics of choice into the vitreous cavity. Intraocular lens (IOL). (Art from Jaypee Highlights Medical Publishers.)



Endophthalmitis After Penetrating Trauma

Patients with penetrating ocular trauma are at risk of developing endophthalmitis and are usually treated with broad-spectrum intravenous antibiotics for several days. If possible, a sample of the intraocular fluid should be sent for culture at the time of surgical repair. The patient who has undergone penetrating trauma should be closely observed in the first few days after the injury and repair for evidence of a developing infection. Patients who have suffered a penetrating ocular injury with a low velocity foreign body in an agricultural or rural setting are at the greatest risk for infection.

Infection in an injured eye can be difficult to distinguish from the severe inflammation that often accompanies trauma to the eye. However, if a crescendo pattern of inflammation or pain is observed, Gram stain should be performed in search for gram-positive bacillus species, Gram-positive and Gram-negative rods, and fungi. Endophthalmitis

from bacilli is particularly fulminant and can lead to total destruction of the eye within 24 hours. It typically presents with severe pain early following repair. In any patient who develops severe pain after trauma, the diagnosis of bacillus endophthalmitis should be excluded in the absence of other definable causes. Recent reports have demonstrated that early intervention with a combination of vancomycin and gentamicin, or clindamycin and gentamicin can preserve the functional integrity of the eye.

TREATMENT OF ENDOPHTHALMITIS

A. Acute Postoperative Endophthalmitis

The Endophthalmitis Vitrectomy Study (EVS) was a randomized, multicenter clinical trial supported by the National Eye Institute that gave solid data on the role of pars plana vitrectomy and of systemic antibiotics in the management of acute endophthalmitis after



cataract surgery or intraocular lens implantation. It provides a framework by which this group of patients can be managed successfully. Immediate vitreous tap without vitrectomy and with intravitreal antibiotic injection was found to be as efficacious as immediate vitrectomy and intravitreal antibiotic injection in cases where the presenting visual acuity was hand motions or better. In cases where the presenting acuity was light perception without hand motions, urgent vitrectomy resulted in a three times better rate of achieving visual acuity of 20/40 (33% versus 11%) and less than half the rate of deteriorating to less than 5/200 (20% versus 47%). The intravitreal antibiotics used were vancomycin 1.0 mg in 0.1 ml and amikacin 0.4 mg in 0.1 ml, and the concentrations did not vary between the vitrectomized and non-vitrectomized eyes. Treatment with intravenous ceftazidime and amikacin (or oral ciprofloxacin and amikacin) had no beneficial or adverse effect when intravitreal antibiotics were used.

In applying the results of the EVS, we suggest caution in making generalizations to other forms of endophthalmitis. The pathogens cultured in the EVS were bacteria of low-virulence associated with routine anterior segment surgery. Of the positive cultures, 90% were single organism Gram positives, and 68% were coagulase-negative. Only 6% were Gram-negative, all of which had media that was too opaque to allow visualization of a retinal vessel. Infections associated with filtration blebs or trauma yield a higher incidence of more virulent organisms such as *Bacillus cereus*, *Streptococcus*, *Haemophilus influenzae*, and Gram-negatives.

In that situation, earlier vitrectomy may have a more important role in saving vision.

The criteria set by the EVS serve as a guideline that should be modified by the clinical circumstance. In general, cases in which the ocular media are clear enough to allow visualization of the optic nerve and retinal vessels do not require vitrectomy and fare well with vitreal tap and injection. However, if the endophthalmitis is seen to be hyperacute in its progression and a more virulent organism is suspected, it may be prudent to perform a vitrectomy to mechanically remove the bacteria, especially if the operating theater is available without delay. Under such controlled circumstances, the EVS showed that the incidence of complications such as retinal detachment or phthisis with pars plana vitrectomy does not exceed that with vitreous tap and injection. Remember though, that visual prognosis relates most directly to the visual acuity at the time of therapy. Treatment of a rapidly deteriorating eye should never be delayed by unavailability of the operating theater, and it is certainly reasonable to perform a tap-inject procedure in the office with the thought of later proceeding to vitrectomy once it becomes possible.

Since Campochiaro showed macular infarction with Amikacin, many surgeons and institutions have shifted to the safer ceftazidime notwithstanding EVS insistence on merits and safety of Amikacin. It may definitely be used; but probably it is wise not to repeat it quickly, especially with vitrectomy, which increases the drug activity on retina.

In our clinical practice, in cases where gram-negative infection is not suspected, we usually substitute ceftazidime 1 mg in 0.1 ml for amikacin in order to reduce the potential for macular toxicity. Further, in order to decrease the retinal damage caused by inflammation, intravitreal dexamethasone in doses of 400 to 800 ug is given where fungal infection is not suspected. If the timing or clinical scenario suggest fungus, then amphotericin 5 ug in 0.1 ml is given and steroids are withheld.

As per the current knowledge, vancomycin is the single most suitable drug for acute, subacute, and selected cases of chronic endophthalmitis. While vancomycin and ceftazidime / amikacin is the preferred combination in acute endophthalmitis; even cefazoline and gentamicin (100 mg, not 400 mg in 0.1 mL) will do, when nothing else is available.

However, if repeat injections are required gentamicin / amikacin should be avoided. However, in cases with vision better than PL, even if intravitreal antibiotics successfully destroy the bacteria, the retina may continue to be damaged by the remaining inflammatory debris, and functional recovery is limited by potentially preventable pathologies such as macular edema. Early vitrectomy is mandatory in advanced cases.

As in the EVS study, we recommend injection of antibiotic into the anterior vitreous at the end of the vitrectomy, thereby avoiding placement of antibiotic in the irrigating fluid. A simple vitrectomy is performed without aggressive attempts to detach the posterior hyaloid or peel pre-retinal membranes.

Cutting and pulling of vitreous adjacent to inflamed or necrotic retina predisposes

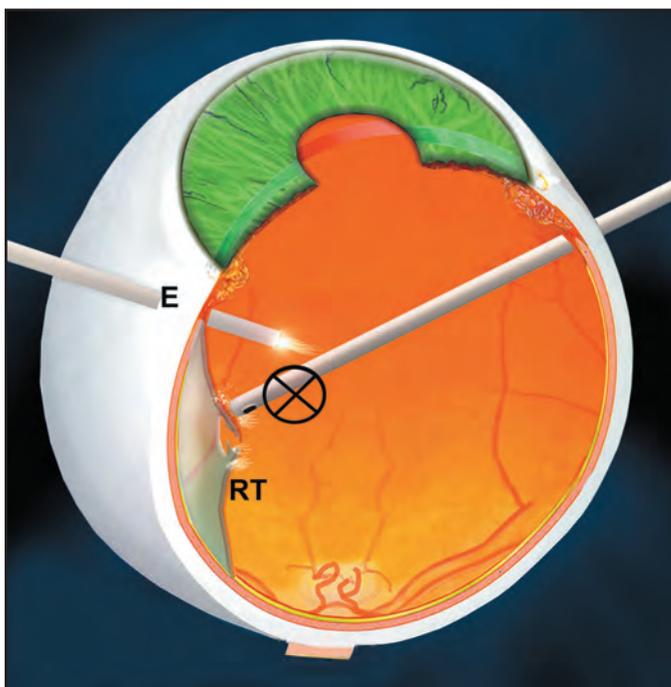


Figure 3: Postoperative Endophthalmitis. A simple vitrectomy should be performed without aggressive attempts to detach the posterior hyaloid or peel pre-retinal membranes in advanced stages. Cutting and pulling of vitreous adjacent to inflamed or necrotic retina predisposes to retinal tears (RT). Because visualization is often limited by corneal opacity, care is taken to avoid risky manipulations. Endoillumination (E). (Art from Jaypee Highlights Medical Publishers.)



to retinal tears that are usually difficult to repair (Figure 3). Because visualization is often limited by corneal opacity, care is taken to avoid risky manipulations. As in the EVS, we have not seen toxicity of antibiotics in vitrectomized eyes when concentrations proven to be safe in non-vitrectomized eyes are used.

The rare situation in which a rhegmatogenous retinal detachment occurs simultaneous with endophthalmitis is worthy of special mention because of its dismal prognosis. In that circumstance, the incidence of proliferative vitreoretinopathy is high and we advocate a careful but aggressive dissection of membranes and use of a long-acting retinal tamponade, usually silicone oil. Antibiotics are placed in the balanced salt infusion prior to the air-fluid exchange in order to ensure a safe concentration on the retina.

B. Acute Postoperative Endophthalmitis in the Non-Cataract/IOL Setting

Bleb Associated Endophthalmitis

In the era of full thickness filtration procedures, the reported rates of endophthalmitis were as high as 9%. After the introduction of partial thickness sclerotomies, the rates decreased to 0.3-1.5%. There is an increased risk of late endophthalmitis associated with inferiorly positioned trabeculectomies. The use of antiproliferative agents (5-fluorouracil and mitomycin C) improved the success rate of glaucoma filtering surgery but was

associated with increased susceptibility to bleb infection. The antiproliferative agents are thought to disrupt conjunctival epithelial and stromal morphology which reduces the filtering bleb's resistance to transconjunctival bacterial migration.

The hallmark of isolated bleb infection is a mucopurulent infiltrate within the bleb, associated with conjunctival epithelial defect and localized conjunctival hyperemia. There may be variable anterior segment inflammation; early on, the vitreous may remain quiet clinically and acoustically.

The bacteria associated with bleb related endophthalmitis must be capable of penetrating intact conjunctiva overlying filtering blebs. Encapsulated organisms such as *Streptococcus* species and *Haemophilus influenzae* are prevalent.

Bleb-associated infection is classified according to severity. In stage I, bleb purulence may be accompanied by mild iridocyclitis. In stage II, moderate iridocyclitis is present. In stage III there is bleb purulence with marked anterior segment inflammation or vitritis.

Bleb cultures guide the antimicrobial choice, with more aggressive therapy for blebs infected with *Streptococcus* and *Haemophilus*, which are associated with worse visual outcomes. Cultures from the surface of the conjunctiva correlate poorly with results of anterior chamber and vitreous aspirates.

Stage I and II disease can be managed on an out-patient basis with aggressive fortified topical, periocular and systemic antibiotics (usually a fluoroquinolone such as ciprofloxacin or



levofloxacin because of their high absorption with oral administration and good penetration into the eye). The choice for fortified topical antibiotics includes vancomycin and ceftazidime (both act synergistically by inhibiting biochemical pathways of bacterial cell wall synthesis). Topical fortified aminoglycosides are recommended over fluoroquinolones because of the lower observed rate of acquired bacterial resistance. Cases that fail to respond or show progression are treated as stage III disease.

In Stage III, immediate hospitalization with vitreous biopsy for culture and intravitreal antibiotic injection is recommended (vancomycin 1mg/0.1 ml, Ceftazidime 2.25mg/0.1 ml and dexamethasone 0.4 mg/0.1 ml) together with topical and peri-ocular antibiotics.

The results of the EVS do not apply to bleb-associated endophthalmitis because of the low percentage of Streptococcus species and gram-negative cases in the study.

Post Traumatic Endophthalmitis

Endophthalmitis is a particular devastating complication of posterior penetrating ocular trauma, affecting between 2-48% of eyes with these injuries. Gram negative organisms are implicated in 8-25% of cases of post-traumatic endophthalmitis. Bacillus species are commonly identified after injuries that involve farm material, so a high index of suspicion should be maintained in this clinical setting. These are ubiquitous gram positive spore forming rods that produce a fulminant en-

dophthalmitis that frequently results in loss of the eye.

Risk Factors include the presence of a low velocity intraocular foreign body (incidence of 6.8%), increased age of patient (> 50 years) as well as a delay of more than 24 hours in primary repair which causes a four-fold increase in the risk of infectious endophthalmitis (3.5% vs. 13.4%). Injuries contracted in rural settings have a higher incidence of endophthalmitis than those occurring in urban locations.

Indications for Treatment Include the Following

1. Inflammatory signs (including the development of a corneal ring abscess) and pain in excess of what is expected based on the injury and repair.
2. The culture results yield a virulent organism.
3. High risk cases with soil contamination or "dirty" intraocular foreign bodies, regardless of the severity of inflammation on initial examination. In such cases, urgent pars plana vitrectomy and intravitreal antibiotic injection are required.

An aggressive approach to suspected traumatic endophthalmitis is important. The Endophthalmitis Vitrectomy study (EVS) recommendations can not be generalized to the post traumatic settings because more virulent organisms are likely to be encountered.

Treatment involves immediate vitrectomy with cultures and debridement of necrotic tissue and removal of any intraocular foreign body. This is accompanied by the administra-



tion of systemic, subconjunctival, intravitreal, and topical antibiotics. Vitrectomy allows the concomitant treatment of intraocular effects of trauma such as retained lens cortex, vitreous hemorrhage and retinal breaks, as well as removal of infected vitreous and bacterial toxins. The choices for intravitreal antibiotic include vancomycin and aminoglycoside (gentamicin or amikacin) if *B. cereus* is cultured.

Although the EVS did not demonstrate benefit for intravenous antibiotic for post-operative endophthalmitis, systemic intravenous antibiotic are considered standard care in post-traumatic endophthalmitis. The role of prophylactic intravitreal antibiotics in penetrating ocular trauma cases is controversial, with no prospective clinical studies published.

The visual prognosis is poor due to structural damage to the eye from the original injury and the increased virulence of organisms associated commonly with traumatic endophthalmitis.

C. Treatment of Chronic Postoperative Endophthalmitis

Delayed onset endophthalmitis occurs six weeks to many months after the initial anterior segment procedure, often as the post-operative anti-inflammatory and antibiotic drops are being weaned. In general this situation is caused by less virulent organisms such as *Propionibacterium acnes*, non-virulent *Staphylococcus epidermidis*, *Candida* species, *Corynebacterium diphtheriae*, and *Listeria monocytogenes*. These cases were not studied in the EVS. They can be associated with low-grade iridocyclitis and vitritis, mutton

fat keratic precipitates, vitreous fibrin strands, and cystoid macular edema. Especially in cases of *P. acnes*, one may find retained lens material and white plaques of bacteria on the intraocular lens or within the capsular bag. The interval between surgery and presentation, and the severity of the symptoms often correlate with the virulence of the organisms. Many of these infections mimic an immune-mediated process, and respond to topical steroids or antibiotics. Although they usually recur once the agents have been stopped, there have been well documented indolent infections with *S. epidermidis* and *P. acnes* that have been cured effectively with good visual outcome using a few weeks of topical antibiotics alone. There is generally no harm to attempting this conservative approach as long as the patient can be followed closely. However, when this approach fails, we generally favor a thorough vitrectomy procedure over tap / injection for several reasons. A larger volume of material can be obtained for culture, giving a higher rate of positive identification of these fastidious organisms. Also, this approach allows biopsy and removal of plaque material in which *P. acnes* often reside, and access to organisms that may be sequestered in the capsular bag. Finally, there can be advantages to mechanical removal of the organisms that have a long replication phase and are less likely to respond completely to a single dose of intravitreal antibiotics. As in the acute cases, it is important to obtain fluid from both the anterior chamber and vitreous cavity for culture, and to incubate samples in anaerobic broth and Sabouraud's nutrient agar for two to four weeks to allow adequate growth. It has been our practice to try to retain the intraocular lens initially in most of these cases, but to remove it with



a secondary procedure if the inflammation persists.

D. Treatment of Fungal Endophthalmitis

Fungal infection is likely to occur in the setting of a debilitated or immunocompromised host, intravenous drug abuse, intravenous catheters, trauma that involves the entry of vegetation into the eye, contaminated irrigating solutions, and in tropical climates where fungi may enter as a contaminant. Because fungi replicate slowly in the early stages, they usually do not present until two or three weeks have elapsed from the initial event. The infection can mimic a chronic bacterial endophthalmitis. Later, the fungus may incite a severe inflammation with vitreous opacities in a string-of-pearls appearance and posterior abscess. In endogenous cases, discussed below, rapidly multiplying chorioretinal infiltrates may be present.

The prognosis largely depends on which species is isolated. *Candida albicans* accounts for over two thirds of fungi, and can usually be eradicated with sequential injections of amphotericin B in doses of 5 to 10 ug every 48 to 72 hours. Because of the potential for severe retinal toxicity, this drug should be delivered slowly into the central vitreous cavity, well away from the posterior pole. In the setting of endogenous disease, especially with intravenous drug abuse or hyperalimentation, systemic candidemia is often present, and therapy with intravenous amphotericin B is recommended. If chorioretinal infiltrates are present with minimal vitreous involve-

ment, then intravenous therapy alone may suffice. Fluconazole is a triazole with excellent penetration into ocular tissues that can be administered orally. It is effective against candida species and is well tolerated with minimal side effects. It can be used in a combination with amphotericin in severe cases and as an alternative in cases of toxicity or intolerance.

Aspergillosis, the most common fungal infection in tropical climates, has unfortunately a grimmer prognosis. It can also be seen in immunocompromised patients after transplantation, patients with leukemia, intravenous drug abusers, and patients with endocarditis or chronic pulmonary disease, especially after treatment with corticosteroids. Visual prognosis is poor, partly because of the propensity for endogenous disease to involve the macula with chorioretinal and subhyaloid abscesses. The layering of white cells under the retina or internal limiting membrane can give a "pseudohypopyon" appearance. Treatment is similar to candidiasis but with a lower threshold for vitrectomy to debulk the fungal load. Itraconazole or Fluconazole should be considered for adjunctive systemic therapy, but the prognosis is poor overall.

Additional organisms that can cause endogenous fungal endophthalmitis include *Coccidioides immitis*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Blastomyces dermatitidis*. It is important to realize that in all of these infections, there is a high incidence of bilateral involvement and disseminated systemic disease that must be investigated, and that mortality has exceeded 10% in some reports.



E. Non-fungal Endogenous Endophthalmitis

Although fungi are the leading cause of endogenous endophthalmitis, bacterial infections occur in a minority of cases. The bacteria reach the eye from a distant focus of infection or from a contaminated intravenous needle or catheter. A wide variety of pathogens have been documented and include *Bacillus cereus*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Neisseria meningitidis*, and *Propionibacterium acnes*. Greenwald's classification divides the condition into anterior focal, posterior focal, anterior diffuse, and posterior diffuse forms. If the disease is anterior and the vitreous cavity is not heavily involved, prompt treatment with intravenous antibiotics can result in recovery of vision. This is also true when a focus of infection is located in the retinal circulation before it has broken into the vitreous and disseminated. However, posterior diffuse disease, often the result of emboli into the central retinal artery, is usually associated with severe ischemia, necrosis, and loss of any meaningful vision.

The clinician must retain a high index of suspicion for this diagnosis and treat it as an ocular emergency. Cultures should be obtained from both the anterior and vitreous cavity, unless the infection is relatively

confined to only one area. Paracentesis can be performed with a short 23 or 25 gauge needle through the limbus or pars plana, with removal of 0.1 ml of aqueous or 0.3 ml of vitreous fluid. If a focal abscess is present anteriorly, then an attempt should be made to aspirate it while keeping the needle over the iris to avoid injury to the crystalline lens (Figure 4). Blood cultures are also warranted. Unlike exogenous bacterial endophthalmitis, prompt and intensive intravenous antibiotics guided by infectious disease consultation are the mainstays of therapy. The consultant may also guide a search for occult distant infections in areas such as the urinary tract, heart valves, joints, skin, liver, and lungs. Topical and subconjunctival antibiotics may be useful for anterior segment disease but have no role in isolated posterior disease. Timing of surgical management with pars plana vitrectomy is controversial, but has a definite role when there is severe vitreous involvement. The usual intraocular antibiotics are recommended for injection into the mid-vitreous: vancomycin 1.0 mg and ceftazidime 1.0 mg or amikacin 0.4 mg, with or without dexamethasone 0.4 mg.

Although prognosis depends in large part on factors outside the clinician's control, such as virulence of the organism, immune status of the host, and size and location of the inoculum, the speed of recognition and intervention with antibiotics are the most important variables that we can control.

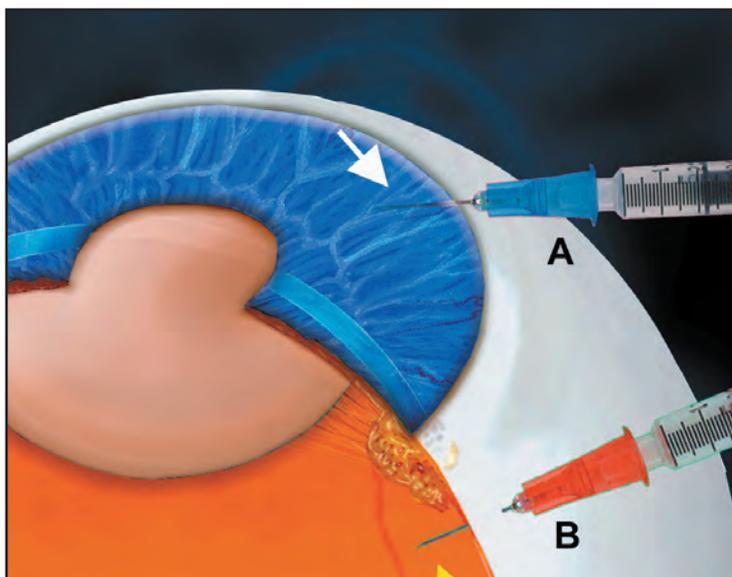


Figure 4: Vitreous Tap from Anterior or Posterior Segment. Cultures should be obtained from both the anterior and vitreous cavity, unless the infection is relatively confined to only one area. Paracentesis can be performed with a short 23 or 25 gauge needle through the limbus (A) or pars plana (B), with removal of 0.1 ml of aqueous or 0.3 ml of vitreous fluid. (Art from Jaypee Highlights Medical Publishers.)

F. Surgical Strategies in Vitrectomy for Endophthalmitis

Endophthalmitis in the acute setting poses challenges to the vitreoretinal surgeon that can be overcome by a thoughtful approach. Often the procedures are done urgently, after hours, when an experienced ophthalmic support staff may not be available. If vitreous tap with antibiotic injection is planned, this can be done expeditiously in the clinic or minor operating room, but formulation of antibiotics at the appropriate dose becomes the greatest concern. If a decision has been made for vitrectomy, the patient should be transported without delay to the nearest facility that can provide the essential equipment.

If the patient is young and in good health, general anesthesia is often preferred. The inflamed eye is often painful and dif-

ficult to anesthetize with local techniques. Further, tissues will have a greater tendency to bleed, extending the duration of the procedure. Given the recommendations of the EVS above, it is more likely that patients going to surgery will have severe media opacity limiting intra-operative visualization. Fibrin membranes may cover the pupil and both surfaces of the intraocular lens, and the cornea may become opaque. Blind maneuvers can result in irreparable damage, so a careful and planned approach is helpful.

At the outset, the integrity of previous surgical wounds should be confirmed, and sutures added as needed to establish a good seal. If a pars plana infusion cannula is to be used, it is best placed at the beginning of surgery while the eye is still firm and entry is easy. Irrigation should not be used, however, until the cannula tip can be visualized within the vitreous cavity. Before then,

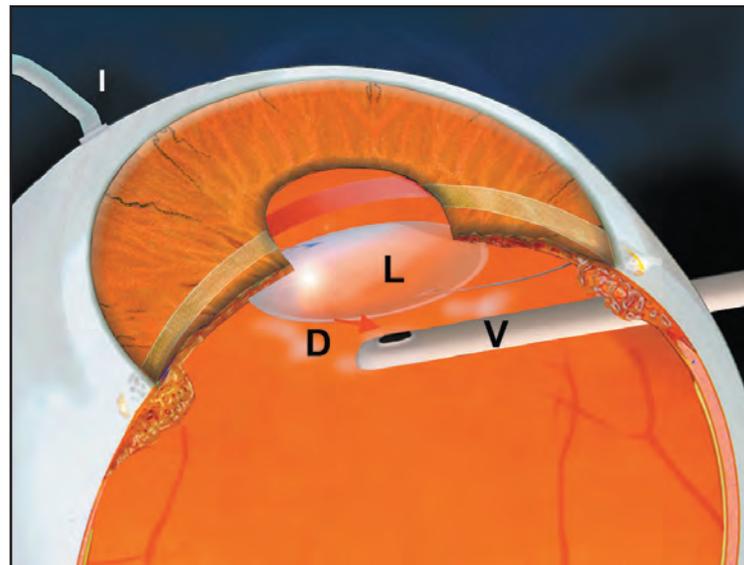


irrigation can be maintained safely through an anterior chamber cannula or bent needle placed through the limbus and in front of the IOL. Fibrin membranes can then be peeled anteriorly using a cystotome, intraocular forceps, or the vitreous cutter. Opaque debris in the anterior vitreous can also be removed safely by placing the vitreous cutter through the pars plana and behind the IOL, while illumination is provided by the microscope (Figure 5).

Dry vitrectomy is performed to obtain a specimen for culture before infusion is initiated. A small syringe is connected by a short piece of tubing to the outflow port of the vitreous cutter. The surgical assistant is asked to aspirate a small sample, typically 0.3 cc, while the cutter is active at high speed and maintained in the central cavity.

If the infection is severe enough to opacify the cornea, a central button may be removed with a trephine. One may pre-place a Flieringa ring and proceed with an open-sky vitrectomy to remove the central vitreous debris; alternatively, a temporary keratoprosthesis can be placed for closed vitrectomy. If the irrigating cannula cannot be visualized, one safe alternative is to place an end-irrigating light pipe into the mid-vitreous cavity. When switching from a limbal to pars plana irrigation system, it is desirable to have dual sources of fluid to avoid hypotony with chamber collapse and possible hemorrhage. A gentle vitrectomy is then performed from anterior to posterior, with attempts to remove pockets of loculated, purulent matter but without efforts to shave to the vitreous base or remove all the peripheral cortical vitreous. The inflamed posterior hyaloid can be tightly adherent to

Figure 5: Posterior Segment Opacification. Irrigation by the infusion cannula (I) should not be used until the cannula tip can be visualized within the vitreous cavity. Before then, irrigation can be maintained safely through an anterior chamber cannula or bent needle placed through the limbus and in front of the IOL. Fibrin membranes can then be peeled anteriorly using a cystotome, intraocular forceps, or the vitreous cutter. Opaque debris in the anterior vitreous (D) can also be removed safely by placing the vitreous cutter through the pars plana (V) and behind the IOL(L), while illumination is provided by the microscope. (Art from Jaypee Highlights Medical Publishers.)





the posterior retina, and we do not recommend attempts to force its separation because of the high risk of retinal tears.

Although the classic teaching has been to do a controlled central core vitrectomy due to concerns about creating peripheral breaks in inflamed retina and also the media not being so clear, more and more people are now advocating a more aggressive approach to vitrectomy for endophthalmitis. Extensive central and peripheral vitrectomy is done followed by a silicon oil tamponade which would prevent fluid collection through any hidden break till the time the Inflammation settles and allows good visibility to treat further. Despite the poor visual prognosis of endophthalmitis surgery, more radical intervention can increase the chance of surgical success and decrease the number of additional procedures in eyes with postoperative endophthalmitis. The silicon oil also compartmentalizes the infection and being inert has less chances of causing any reaction to itself. However, though EVS advocated only 50% vitrectomy for endophthalmitis but the EVS reports that 10.5% of cases required an additional procedure within 7 days of entry into the study. In 25% of patients, a late additional procedure was required and was performed more than 7 days after study entry. At the final examination, 3% had phthisis. During the entire study, additional surgery was performed in 34% of patients. However, despite the relatively poor visual prognosis of endophthalmitis surgery, total PPV with buckling surgery, silicone tamponade, and endolaser increases the chance of surgical success and decreases the number of additional procedures in eyes with severe postoperative endophthalmitis.

In the setting of trauma, a more thorough exploration is warranted to remove any intraocular foreign bodies. If the crystalline lens has been violated, then complete removal is recommended using the vitreous cutter or fragmatome from a pars plana approach. Depending on the clinical circumstances, prophylactic intraocular antibiotics, typically in half the usual therapeutic dose, may be administered. Because of possible break down of the blood-retinal barrier, systemic antibiotics may have a role in this situation.

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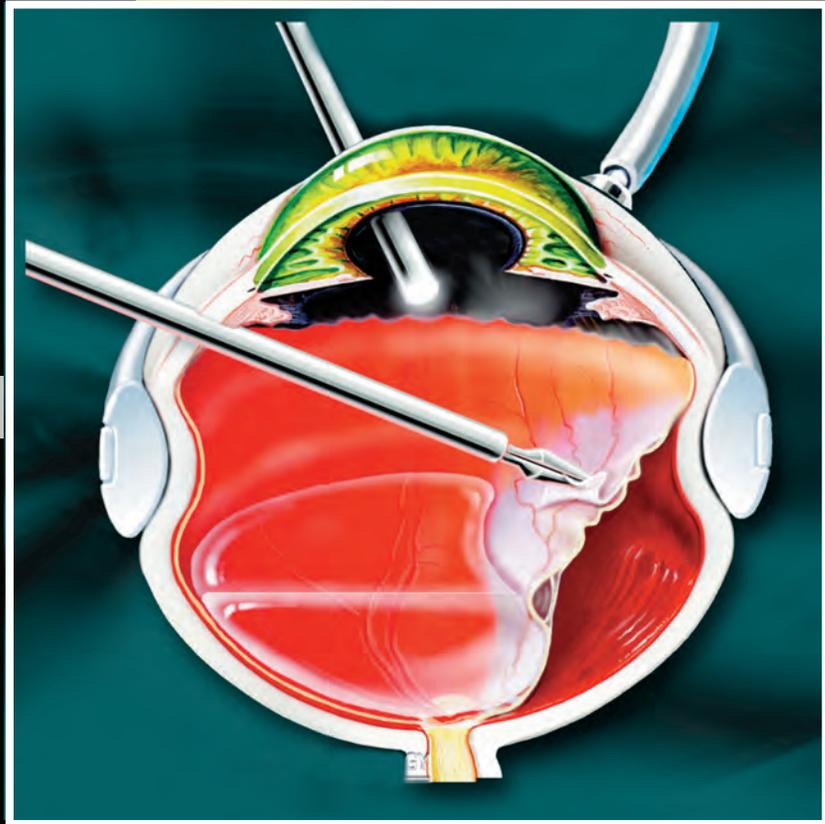
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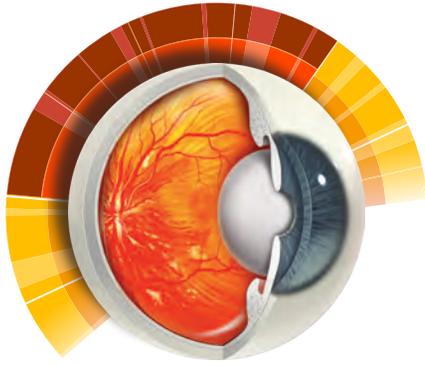


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Section 9

Leading Achievements in Retina



39

Nutrition in Retinal Diseases

KONSTANTINIDIS LAZAROS, MD.,
LEONIDAS ZOGRAFOS, MD

Introduction

Even prior to the invention of the ophthalmoscope in 1851, nutritional deficiencies were known as important causes of vision loss while many case reports and series studies described even by the early part of the 20th century the association of nutritional deficiencies to visual function and eye diseases.¹

However, it has only been the last decades that large population-based studies provided significant evidence that nutrition plays an important role to eye health. An association of nutritional factors to variety of retinal diseases has been made suggesting that nutritional supplementation or specific dietary modifications may potentially influence the course of these diseases. According to these studies nutrition seems to play an essential role to age-related macular degeneration (AMD), diabetic retinopathy and retinal vascular diseases.

Evidence concerning the role of nutritional factors for these diseases is assessed in this chapter.

Nutrition and Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a leading cause of blindness.²

The prevalence of AMD and its resultant morbidity is likely to increase in the future. Changes in nutritional behavior such as greater intake of dietary antioxidants may contribute to lower future rates of AMD incidence and progression according to forecasting models of incidence of AMD.³

Currently there are three main theories for retinal changes associated with non-exudative stages of AMD: the oxidative stress theory, the choroidal circulation theory and the degeneration of Bruch's membrane theory. Nutrition factors may play a role in all of these theories.⁴

The oxidative stress hypothesis for the etiology of AMD is based on the breakdown of protective antioxidant systems within the retina, possibly induced or influenced in some cases by insufficient diet.



The choroidal circulation theory hypothesize that removal of waste materials and the supply of nutritional substances as well as oxygen exchange to the neural retina is impaired due to choroidal vascular alterations that lead to AMD alterations.

Finally, age-dependent changes in Bruch's membrane are considered to compromise transport of nutrients and metabolic substances from and to the RPE. Consequently it is considered that degeneration and thickening of Bruch's membrane initiate or at least contribute to AMD.

Several studies have demonstrated that various dietary components may affect retinal degeneration, and are discussed in this section.^{5, 6}

Vitamin C

L-ascorbic acid, or vitamin C, is a water-soluble antioxidant that has been shown to react directly with hydroxyl radicals, superoxide and singlet oxygen. The nutritional supply of vitamin C comes mainly from fruits and uncooked vegetables. Those particularly rich in vitamin C include kiwi, guava, melons, mango, citrus fruits, cabbage and Brussels sprouts⁷ (Figure 1).

It has been hypothesized that vitamin C has an important role as a retinal antioxidant due to its high concentration in the retina. However, epidemiological studies did not provide any clear evidence of relation between vitamin C consumption and AMD consumption.

Data from the first National Health and Nutrition Examination Survey did not demonstrate clearly an inverse association of vitamin C with AMD.⁸



Figure 1: Many fruits like kiwi, guava, melons, mango, citrus fruits, cabbage and brussels sprouts are particularly rich in vitamin C.

In the Eye Disease Case-Control Study Group vitamin C consumption was not associated with a statistically significant reduced risk for AMD, although a possibly lower risk for AMD was suggested among those with higher intake of vitamin C, particularly from foods.⁹

The Beaver Dam Eye Study found no associations between vitamin C intake and the 5-year incidence of early AMD.¹⁰

In the Blue Mountains Eye Study authors reported that increasing total vitamin C intake from diet and supplements, was associated with an increased risk of incident early AMD after the 5-year follow-up,¹¹ however this association could not be confirmed after the 10-year follow-up.¹²

Some studies found that combination of all antioxidant nutrients that include vitamin C might have a protective effect towards AMD.

A protective effect regarding incidence and progression of AMD by combination of anti-



oxidant nutrients that include vitamin C was found in the Age Related Eye Disease Study (AREDS)¹³ and Rotterdam Study.¹⁴ However, the Blue Mountains Eye Study¹² was unable to confirm the protective effect shown on the above-mentioned studies.

Vitamin E

In 1922, vitamin E was first discovered as an essential dietary factor for the reproduction in rats.¹⁵ After the isolation of pure vitamin E from cottonseed oil, the name tocopherol was proposed, from the Greek, tokos (offspring) and pherein (to bear).¹⁶ The richest food sources of vitamin E are certain oils, such as wheat germ oil, sunflower oil and sunflower seeds, almonds, peanut butter, wheat germ and margarine (Figure 2). Vitamin E is essential for maintaining a healthy retina. Patients with inherited abetalipoproteinemia, a disorder in which fat-soluble vitamins, including vitamin E, cannot be sufficiently absorbed, develop retinal

degeneration. Supplementation of vitamin E, however, can prevent retinal degeneration in this pathological condition.^{17, 18}

Vitamin E is thought to function as an antioxidant and appears to protect polyunsaturated fatty acids from oxidative damage. A-tocopherol is the dominant variant of vitamin E in human retina with highest concentration in the retinal pigment epithelium (RPE).¹⁹ Photoreceptor outer segments are rich in polyunsaturated fatty acids, and therefore it has been hypothesized that α -tocopherol might play a significant role as an antioxidant in the retina. Several animal studies have demonstrated the antioxidant effect of vitamin E in retina.²⁰⁻²² However, the current findings of the epidemiological studies on a possible association between increasing total vitamin E intake and AMD risk also are inconsistent with studies that have reported a protective effect on AMD progression¹³ or development,^{10,14} no effect^{9,11,23-26} or a negative effect.¹² More precisely, Taylor et al in a large



Figure 2: The richest food sources of vitamin E are certain oils, such as sunflower oil and sunflower seeds, almonds, peanut butter, wheat germ and margarine.



study on the role of vitamin E that included about 1000 participants concluded that daily supplement with vitamin E does not prevent the development or progression of early or later stages of age related macular degeneration.²⁶ This is probably the only large-scale study that investigated the role of vitamin E on AMD as a sole supplement without combining other antioxidants.

In the Blue Mountains Eye Study at 10 years follow-up higher intakes of total vitamin E predicted late AMD.¹² This is the only study reporting a harmful effect of dietary vitamin E on AMD risk.

The multicenter Eye Disease Case-Control Study vitamin E consumption was not associated with a statistically significant reduced risk for AMD.⁹

In the in the Rotterdam Study intake of vitamin E was associated with a substantially reduced risk of AMD in elderly persons.¹⁴

The AREDS study demonstrated reduction for the development of advanced AMD with a combination of antioxidants containing vitamin E.¹³ However, no conclusion, can be drawn for the effect of vitamin E alone.

Carotenoids

There is increasing evidence that antioxidant properties of carotenoids have a protective role in the retina. The three major carotenoids that have been related to AMD are lutein, zeaxanthin and β -carotene.

β -Carotene

β -Carotene, a hydrocarbon carotenoid, is one of the major carotenoid precursors of vitamin A and it has been shown to be an effective antioxidant.^{27,28} Beta-carotene is a quencher of singlet oxygen radicals, in contrast to vitamin A, which has only a very small capacity to scavenge free radicals. In the eye it is mostly found in the retinal pigment epithelium/choroid and not in the overlying retina.²⁹

Dietary sources of β -Carotene are principally marigold flowers, dark green vegetables and colored fruit. Typical examples include carrots, pumpkins, spinach, beans, apricots and peaches^{30,31} (Figure 3).

Its been advocated that low serum levels of carotenoids are related to a higher risk of AMD³² and higher serum levels to a lower risk of different stages of AMD.^{33,34}



Figure 3: Dietary sources of β -Carotene are principally marigold flowers, dark green vegetables and colored fruit. Typical examples include carrots, spinach and beans.



In the Beaver Dam Eye Study intakes of pro-vitamin A carotenoids were inversely related with the incidence of large drusen.¹⁰

Another study showed no beneficial effect of long-term supplementation with beta-carotene on the occurrence of AMD among smoking males.³⁵

In the Blue Mountains Eye Study at 10-years follow-up higher beta-carotene intake either from diet alone or from diet and supplements combined was associated with an increased risk of AMD.¹² On the other hand the Age Related Eye Disease Study (AREDS) showed a significant reduction in ARMD progression with a combination of various antioxidant supplements that included 15 mg of β -carotene daily.¹³ This study however, was not designed to study the role of beta-carotene supplementation alone.

The role of β -carotene on AMD has to be further defined. Furthermore, an important risk of higher risk for lung cancer has been related to high intake of β -carotene (20–30 mg/day) in smokers.^{36–38} These reports should be taken in consideration when prescribing supplements containing high doses of β -carotene and smokers should avoid beta-carotene supplementation.³⁷

Lutein and Zeaxanthin

Lutein and zeaxanthin are the only carotenoids that concentrate in the macula, where they are the main components of macular pigment (MP).^{39–41} The concentration of lutein is greater than that of zeaxanthin in the peripheral region of the macula and zeaxanthin is more abundant in the central region.^{42,43} Due to this distribution pattern in the retina it has been suggested that the

role of lutein is focusing on protecting the rods concentrated in the peripheral retina while zeaxanthin on protecting the cones concentrated in the central retina.^{44,45,46}

Functions of MP include quenching free radicals and thereby acting as an antioxidant to protect the macula from oxidative damage,^{47–50} filtering blue light,⁵¹ and increasing stability of lipid membranes by modifying their structural and dynamic properties.⁵²

The pathogenesis of AMD is likely to involve a complex interaction of cellular and vascular factors, which may be promoted, between others, by light damage⁵³ and oxidative stress.⁵⁴ Therefore, it has been hypothesized that intake of lutein and zeaxanthin might have a protective effect on the development and/or progress of AMD.

There are currently no dietary reference intakes for carotenoids. In the United States, the average daily intake for lutein and zeaxanthin is 2.0–2.3 mg/d for men and 1.7– 2.0 mg/day for women. Lutein and zeaxanthin are present in a wide variety of plant sources, such as leafy green vegetables (kale, turnip, and spinach etc.), fruits like peaches, oranges, mangos, papaya, and kiwi, as well as a few animal sources, such as egg yolk^{46,55} (Figure 4).

A relative decrease of these carotenoids has been shown in eyes of patients with AMD,⁵⁶ and a higher intake of lutein and zeaxanthin from foods or supplements increases serum levels of these carotenoids and macular pigment density in humans.^{57–59} A role for dietary intake of lutein and zeaxanthin in AMD prevention is supported further by animal models.^{60–62} However, studies on the association between dietary, or serum levels,



Figure 4: Lutein and zeaxanthin are present in a wide variety of plant sources, such as leafy green vegetables (kale, spinach etc.), fruits like oranges, mangos and kiwi, as well as a few animal sources, such as egg yolk.

of lutein and zeaxanthin and AMD have been inconsistent.¹²

The Veterans LAST study (Lutein Antioxidant Supplementation Trial), a 12-month randomized trial of lutein and antioxidant supplementation in people with atrophic age-related macular degeneration demonstrated that daily 10-mg lutein supplements, with or without additional nutrients, improved visual function.⁶³

In the Carotenoids in Age-Related Eye Disease Study (CAREDS) that included 1787 participants it's been demonstrated that diets rich in lutein plus zeaxanthin may protect against intermediate AMD.⁶⁴

In the third national health and nutrition examination survey, a large, six-year study involving 8,222 subjects over the age of 40, higher levels of lutein and zeaxanthin in the diet were related to lower odds for pigmentary abnormalities as sign of AMD.⁶⁵

In another study Gale et al. reported a significant association between low plasma levels of zeaxanthin and the presence of AMD; no such association was noted for lutein. The authors suggested that zeaxanthin might be more protective than lutein.⁶⁶

In the POLA study the highest quintile of plasma zeaxanthin was significantly associated with reduced risk of AMD. AMD was significantly associated with combined plasma lutein and zeaxanthin and tended to be associated with plasma lutein.⁶⁷

The Blue Mountains Eye Study at 10 years follow-up found higher dietary lutein and zeaxanthin intake reduced the risk of long-term incident AMD.¹²

However, In the Muenster Aging and Retina Study (MARS) the serum concentrations of lutein and zeaxanthin were not related to the prevalence of AMD.⁶⁸ Additionally, several other studies have also failed to find a significant association between intake²³ or



serum levels³² of lutein with zeaxanthin with AMD.

Currently, an ongoing study the Age-Related Eye Disease Study 2 (AREDS 2), a multi-center, randomized trial will attempt to assess the effects of oral supplementation of macular xanthophylls (lutein and zeaxanthin) and/or long-chain omega-3 fatty acids on the progression to advanced age-related macular degeneration (AMD).⁶⁹ Enrollment for this study concluded in June 2008 and approximately 4000 participants will be followed between five and six years.

Omega-3 Fatty Acids

There is an increasing interest regarding the role of omega-3 Fatty acids (omega-3FAs) on the retinal function and more specifically on the incidence of AMD.

Omega-3FAs include alpha-linolenic acid (a short-chain omega-3 fatty acid), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) (both long chain omega-3 fatty acids). Alpha-linolenic acid (LNA) is the dietary precursor to both DHA and EPA.^{70,71}

Omega-3FAs are found in seafoods, some plants, and some livestock rations. Fish oils are the only concentrated source of EPA and DHA (Figure 5). The major omega-3FA in plants is LNA.⁷⁰

Very high levels of DHA are present in the retina, specifically in the disk membranes of the outer segments of photoreceptor cells⁷² suggesting that DHA has an important functional role in the retina, although its exact role is not well understood.⁷³



Figure 5: Omega-3FAs are found in sea foods while fish oils are the only concentrated source of docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) (both long chain omega-3 fatty acids).

Omega-3 FAs demonstrate various properties in relation to retinal function. DHA influences the biophysical properties of membranes via its high polyunsaturation and may help to create a membrane that accommodates the dynamic behavior of rhodopsin during the photoreceptive process.⁷⁴ DHA also may play a role in modulating G protein- coupled signaling pathways that are involved in visual transduction.⁷⁵ Furthermore, EPA affects lipoprotein metabolism and decreases the production of compounds that exert pro-inflammatory cellular actions like cytokines, interleukin 1 and tumor necrosis factor.⁷⁶ Considering the possible role of inflammation in the pathogenesis of AMD, it has been hypothesized that EPA may be a protective factor in this disease.⁷⁷

Several animal studies have shown that dietary deprivation of docosahexaenoic acid (DHA), results in abnormal electroretinograms, visual impairment, loss in rod



phototransduction sensitivity and delay in rod recovery that is accompanied by lower retinal levels of DHA phospholipids.⁷⁸⁻⁸⁰

Several studies reported a protective role of omega-3 FAs regarding the incidence or the progression of AMD.

The Report No. 23 of the Age-Related Eye Disease Study (AREDS) suggested that dietary omega-3 long-chain polyunsaturated fatty acid intake was associated with a decreased risk of progression from bilateral drusen to central geographic atrophy.⁸¹

Report 20 from the Age-Related Eye Disease Study (AREDS) describes a 40% to 50% reduced likelihood of having neovascular AMD among participants who reported the highest levels of omega-3 FA consumption.⁸²

The US Twin Study of Age-Related Macular Degeneration concluded that increased intake of omega-3 FA and fish, particularly for 2 or more servings per week and reduced risk of AMD.⁸³

In the Eye Disease Case Control Study, higher intake of omega-3 fatty acids or fish was associated with a lower risk for AMD among individuals consuming diets low in linoleic acid, an omega-6 fatty acid. Conversely, neither omega-3 fatty acids nor fish intake were related to risk for AMD among people with high levels of linoleic acid intake.⁸⁴

In the Blue Mountains Eye Study 40% reduction of incident early AMD was associated with fish consumption at least once a week, whereas fish consumption at least 3 times per week could reduce the incidence of late AMD.⁸⁵

In the Nurses' Health Study and the Health Professionals Follow-up Study that included 42,743 women and 29,746 men aged of more than 50 years, DHA had a modest inverse relation with AMD and more than 4 servings of fish per week was associated with a 35% lower risk of AMD.⁸⁶

The findings from the epidemiologic studies suggest that omega 3-FA may represent an easily implemented approach to modifying risk of AMD progression. The ongoing AREDS II clinical trial may further elucidate the role of omega-3 FA on AMD (<http://www.areds2.org>).⁸⁷

Cofactors of Antioxidant Enzymes

Zinc

The retina and choroid contain the highest concentrations of zinc of any tissue in the human body⁸⁸. Zinc is a cofactor for many enzymes, including copper-zinc superoxide dismutase and is involved in the regulation of catalase activity, two important antioxidant enzyme systems in the retina.⁸⁹⁻⁹¹ Zinc is also a cofactor for vitamin A metabolism and is essential for the synthesis of retinol binding protein.⁹²

It has been demonstrated that zinc protects against oxidative damage in cultured human retinal pigment epithelial cells.⁹³ Furthermore, several animal model studies support a protective role for zinc in AMD.^{91,94} Low levels of zinc in parenteral nutrition in humans led to reversible changes in the electroretinogram.⁹⁵

In a laboratory investigation of eighty-eight donor eyes it was found that levels of zinc and copper on retinal pigment epithelium



and choroid complex were reduced in AMD eyes suggesting that metal homeostasis plays a role in AMD and in retinal health.⁹⁶ However, epidemiologic studies on the association between zinc intake and AMD have been inconsistent.

Stur M. et al. in a 2-year, double-masked, randomized, placebo-controlled study that included 112 participants concluded that oral zinc substitution has no short-term effect on the course of age-related macular degeneration in patients who have an exudative form of the disease in one eye.⁹⁷

Cho E. et al. followed 66,572 women and 37,636 men without AMD at baseline for 10 years and 8 years respectively and concluded that moderate zinc intake, either in food or in supplements, was not associated with a reduced risk of AMD.⁹⁰

On the other hand, however, other studies have reported a protective effect from zinc on AMD.^{10,12-14,23,98,99}

In the 10-year follow-up Blue Mountains Eye Study report, participants in highest decile of total zinc intake (15.8 mg/day) were found to be significantly less likely to develop early or any AMD compared with the remaining population.¹²

In a recent randomized, prospective, placebo-controlled clinical trial of a novel zinc-monocysteine (ZM) compound it was found that 25 mg of ZM twice daily was well tolerated and was associated with improved macular function in comparison to a placebo in persons with dry AMD.⁹⁹

The epidemiologic Beaver Dam Eye Study evaluated zinc intake and macular pigmentary changes and found less prevalent and less newly developed pigmentary abnormalities in participants with higher levels of zinc intake.¹⁰

In the Rotterdam Study that included about 5000 participants at risk of AMD at baseline, a high dietary intake of zinc combined with beta-carotene, vitamins C and E was associated with a substantially reduced risk of AMD in elderly persons.¹⁴

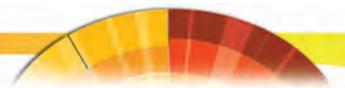
The AREDS included about 80 mg of zinc per day in two of their regimens. One of the four arms of the study supplemented zinc only. In this group the probability of a defined AMD or visual acuity event at 5 years' follow-up was decreased by 6.2 and 3.6% compared to placebo. However, combination with antioxidants further improved the outcome.¹³

Copper

Copper has also a high concentration on retinal pigment epithelium and is a coenzyme for antioxidant enzyme superoxide dismutase, which may play a role in AMD development.¹⁰⁰ Furthermore, copper is involved in the metabolism of the RPE.¹⁰¹ Levels of copper and zinc in the human retina has been associated with cadmium levels a toxic metal with no known physiological function that interferes with copper and zinc metabolism and accumulates in human retinal tissues during aging and might play a role in AMD.⁹²

Copper and zinc levels have been found to be reduced in the retinal pigment epithelium and choroid complex zinc in AMD eyes.⁹⁶

However, clinical studies in humans evaluating copper and AMD are limited. A study suggested a relationship between serum ceruloplasmin, a multifunctional, copper-binding alpha-globulin, trace metals, and the tissue alterations associated with macular degeneration.¹⁰² Copper has been included into the



AREDS treatment arms receiving zinc, not for a potential benefit preventing progression of AMD, but to prevent possible zinc-induced copper deficiency anemia.

Nutritional Risk Factors and AMD

Dietary Fat Intake

It has been suggested that high dietary fat intake may increase the risk for AMD with various mechanisms. Dietary fat has been associated with atherosclerosis and could therefore have a negative effect on blood supply in the choroid and retina. Additionally, increased deposition of fat in Bruch's membrane could adversely affect exchange of nutrients and waste products to and from the retinal pigment epithelium. Finally, high levels of fatty acids might increase oxidative damage due to high susceptibility of fatty acids to oxidation especially under high oxygen tension and light exposure as found in the macula.⁴

Several clinical studies have shown an adverse effect of specific fat intakes on AMD.^{84,86,103-105} Types of dietary fats that are particularly related to an increased risk of progression or development of AMD are saturated, monounsaturated, polyunsaturated, transunsaturated fats and linolenic acid.^{84,90,103}

Seddon J. M. et al. in a multicenter study that among individuals with the early or intermediate stages of AMD, demonstrated that high intake of specific types of fat—including vegetable, monounsaturated, and polyunsaturated fats and linoleic acid, was associated with increase risk of progression to advanced AMD.⁸⁴

In the in the Nurses' Health Study and the Health Professionals Follow-up Study total fat intake was positively associated with risk of AMD.⁸⁶

The Beaver Dam Eye Study evaluated several aspects of dietary fat intake. Participants with high intake of saturated fat and cholesterol were associated with increased risk for early age-related maculopathy.¹⁰⁴

On the other hand, in the Third National Health and Nutrition Examination Survey AMD was not significantly associated with dietary fat intake.¹⁰⁶

There is increasing evidence for a correlation of dietary fat intake and serum cholesterol levels to AMD.^{84,90,105} The Eye Disease Case-Control Study showed people with increased serum cholesterol level to be compared to people with low levels of serum cholesterol at higher risk for neovascular AMD.¹⁰⁷

Several studies indicated that statins used to lower LDL serum cholesterol levels to prevent cardiovascular events, could reduce the risk of especially neovascular AMD.¹⁰⁸⁻¹¹⁰ In the Beaver Dam Eye Study however, no association was found between statin use and incident or progression of AMD over a five-year period.^{111, 112}

Alcohol

It have been suggested that alcohol consumption may have both harmful and protective effects on AMD. Alcohol is a known neurotoxin that can result in oxidative brain damage¹¹³ and thus in heavy amounts may be expected to have an adverse effect on the retina. However, moderate consumption is associated with decreased platelet



aggregation, lower serum fibrinogen levels, lower C-reactive protein concentrations and higher high-density lipoprotein levels¹¹⁴ all of which may be protective for AMD.¹¹⁵⁻¹¹⁷

Chong EW et al. in a systematic review and meta-analysis of observational studies regarding alcohol consumption and the risk of AMD found that heavy alcohol consumption (more than three standard drinks per day) is associated with an increased risk of early AMD.¹¹⁶

The first National Health Nutrition and Examination Survey (NHANES-1) found that moderate wine consumption was associated with decreased probability of developing AMD.¹¹⁸

In the Blue Mountains Eye Study, no relationship was found between beer or wine intake and early or late AMD, but an increased risk of early AMD was found among those who drank spirits.¹¹⁹

In the Beaver Dam Eye Study, alcohol consumption was not related to the 15-year cumulative incidence of AMD.¹²⁰

In conclusion there is currently insufficient evidence regarding the associations between moderate alcohol consumption or different alcoholic beverages and AMD. However, patients seeking advice on AMD prevention should be encouraged to stop heavy alcohol consumption.¹¹⁶

Nutrition and Diabetic Retinopathy

Diabetic retinopathy is a leading cause of visual loss and blindness. The prevalence of

diabetes and consequently its complications as RD is projected to increase worldwide as a result of changing of dietary patterns leading to an obesity epidemic.^{121,122}

Prospective, randomized, long-term clinical trials have demonstrated that tight glycemic control is a key issue in the treatment for diabetic retinopathy.¹²³⁻¹²⁶

More precisely, the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), showed a strong stepwise relation between glycosylated hemoglobin and the incidence and progression of diabetic retinopathy.¹²⁷

Intensive insulin treatment, as practiced in the Diabetes Control and Complication Trial, demonstrated statistically significant reductions in the incidence of (27%) and in progression (76%) of retinopathy.¹²⁸ Additionally, in the United Kingdom Prospective Diabetes Study (UKPDS) intensive blood-glucose control substantially decreased the risk of microvascular complications by 25%.¹²⁹

Appropriate diet in addition to medical treatment is essential to obtain a tight glycemic control. It has been advocated that low glycaemic index diet could lessen risk of diabetic complications.¹³⁰ Recently, it's been promoted that a low-fat vegan diet appeared to improve glycemia and plasma lipids more than did conventional diabetes diet recommendations¹³¹ while increase intakes of carbohydrate, fiber, and several micronutrients.¹³²

A study of 407 diabetic patients in Australia suggested that a Mediterranean-Greek type of diet was protective against diabetic retinopathy.¹³³ The Mediterranean diet is characterized by a high intake of vegetables, legumes, fruits and nuts, cereals, and olive



Figure 6: The Mediterranean-Greek type of diet that characterized by a high intake of vegetables, legumes, fruits and nuts, cereals, and olive oil has been suggested to be protective against diabetic retinopathy.

oil, a moderate intake of dairy products, and a low intake of meat and poultry (Figure 6).

Recently, have been suggested that synergies between carotenoids are implicated in diabetic retinopathy, independent of established risk factors and it has been indicated that dietary modulation of retinopathy risk may be possible by increasing intakes of lutein- and lycopen-rich foods.¹³⁴

However the best dietary regimen for the prevention and treatment of diabetes mellitus and its complications it has not been yet accurately determined.^{135,136}

The role of micronutrients supplementation in reducing the risk of development of diabetic retinopathy has gained increasing attention last years.¹³⁷⁻¹³⁹ Oxidative stress is increased in the retina in diabetes.^{140,141} The possible sources of increased oxidative stress might include increased generation of free radicals or impaired anti-oxidant defence system. Thus, supplementation with anti-oxidants represents an achievable adjunct therapy that may potentially help preserve vision in diabetic patients.¹⁴²

Dietary supplementation with various antioxidants has provided encouraging results in experimental models of diabetic retinopathy.¹⁴²⁻¹⁴⁹

In a recent study, supplementation of taurine in diet of diabetic rats led to lower expression of glial fibrillary acid protein (GFAP) and vascular endothelial growth factor (VEGF) that play a significant role to pathogenesis of diabetic retinopathy. This may have prospective implications of using taurine to treat complications in diabetic retinopathy.¹⁴⁸

In a study on diabetic rats Zinc showed beneficial in both controlling hyperglycemia and the protection of the retina against oxidative stress and development of diabetic retinopathy.¹⁴⁵

Additionally a positive role of vitamin E was demonstrated by several animal studies^{150, 151} that may inhibit progression of diabetic retinopathy by prevention of diabetes-induced abnormal retinal blood flow.¹⁵²

Benfotiamine (a vitamin B1 derivative) was demonstrated experimentally to inhibit progression of diabetic microangiopathy by various mechanisms and might have a role in the prevention and/or treatment of diabetic retinopathy.^{147,153,154}

In another animal study was demonstrated that the long-term administration of alpha-lipoic acid supplementation has beneficial effects on the development of diabetic retinopathy via inhibition of accumulation of oxidatively



modified DNA and nitrotyrosine in the retina and suggested that may help to prevent vision loss in diabetic patients.¹⁴⁶

Another animal study concluded that a mixture of antioxidants including Trolox, alpha-tocopherol, N-acetyl cysteine, ascorbic acid, beta-carotene, and selenium can inhibit the development of the early stages of diabetic retinopathy.¹⁴⁴

A recent study interestingly demonstrated that Age-Related Eye Disease Study-based (AREDS) micronutrients that that were shown to reduce the risk of development of AMD inhibit the development of diabetic retinopathy in rodents by inhibiting oxidative and nitrate stress.¹⁴⁹

Despite the very encouraging results of animal studies regarding the role of micronutrients on reducing the risk of development of diabetic retinopathy existing human clinical trials and epidemiologic studies have been less conclusive.¹⁵⁵⁻¹⁵⁸

Some studies suggested that vitamin C might play a role in microvascular complications of diabetes, but results were ambiguous.¹⁵⁹⁻¹⁶² A large scale, long term epidemiologic study (NHANES III) that involved 998 diabetic found no significant relationship between serum vitamin C concentrations and risk of diabetic retinopathy.¹⁵⁶ Additionally, in the Atherosclerosis Risk in Communities (ARIC) Study that involved 387 participants no significant relationship found between vitamin C intake and diabetic retinopathy.¹⁵⁵ However the San Luis Valley Diabetes Study demonstrated a risk of increased severity of diabetic retinopathy related to an increase dietary intake of vitamin C.¹⁵⁷

Several clinical studies evaluated the role of vitamin E in diabetes and diabetic retinopathy.^{155-158, 163} In a large epidemiologic study that involved 3,654 diabetics vitamin E did not found to have any significant effect on history of laser therapy for diabetic retinopathy.¹⁵⁸ Furthermore, no significant relationships were found between serum α -tocopherol and diabetic retinopathy in NHANES III¹⁵⁶ or between dietary vitamin E intake and diabetic retinopathy in the ARIC study.¹⁵⁵ On the other hand, in the San Luis Valley Diabetes Study, higher dietary intake of vitamin E was associated with an increased risk of retinopathy.¹⁵⁷ Contrarily, a small prospective study of 36 type I diabetics concluded that oral vitamin E treatment appears to be effective in normalizing retinal hemodynamic abnormalities and suggested that vitamin E supplementation may provide an additional benefit in reducing the risks for developing diabetic retinopathy.¹⁶³

Another nutritional elements that was studied in clinical studies is zinc and chromium suggesting a potential beneficial antioxidant effect on diabetic patients of the individual and combined supplementation of these elements that might influence the course of diabetic retinopathy.¹⁶⁴⁻¹⁶⁶

More studies are warranted in order to clarify the role of micronutrients dietary supplements on diabetic retinopathy and although its use in some cases might be potentially helpful it is not currently recommended.⁴

Nutrition and Retinal Vascular Diseases

Nutritional elements have been recently recognized as important risk factors in the



pathogenesis of various retinal vascular diseases. More specifically, nutritional related entities that are related to retinal vascular diseases include hyperhomocysteinemia, disorders of iron metabolism and lipid abnormalities.

Hyperhomocysteinemia is associated in several studies with retinal vascular disease, including central retinal vein occlusion, branch retinal vein occlusion, and central retinal artery occlusion.^{1,167-173}

Several studies have shown that serum or plasma total homocysteine concentrations can be reduced to normal following folate supplementation or a combination of folate and other B vitamin supplements.¹⁷⁴⁻¹⁷⁶

In a study on retinal vein occlusions, Hansen et al.¹⁷⁷ decreased significantly plasma homocysteine in all hyperhomocysteinemic patients by prescribing 5 mg daily of folic acid over at least 2 weeks. Cahill et al.¹⁷¹ concluded assessment of plasma homocysteine and folate levels should be considered for ocular vasculopathic patients. They hypothesized that reduction of plasma homocysteine level by folate supplementation could decrease the occurrence of the disease in the fellow eye or other systemic vascular events and recommended 400 μ m of oral folates daily for patients with elevated plasma homocysteine and low folate levels. However, others consider that there is currently not enough evidence for such a recommendation to be established as a general rule.¹⁷⁸

Finally, it worth mentioning that many studies¹⁷⁹⁻¹⁸³ demonstrated that dietary interventions with vegetables, fruits, wholegrain bread, eggs, chicken, fish, milk and breakfast cereals (Figure 7) were related to an increased folate intake and inversely associated with serum homocysteine levels; thus might potentially contribute to the effort of lowering homocysteine levels on ocular vasculopathic patients.

Other nutrition related diseases that are associated less frequently with vascular retinal diseases include iron deficiency and hyperlipidemia.

Iron deficiency has been related to with background retinopathy,^{184,185} venous stasis retinopathy¹⁸⁶, central retinal artery occlusion,¹⁸⁷ central retinal vein occlusion.^{188,189}

Foods that are rich in iron include liver, beef, veal, fish, eggs, soya bean, broccoli and green beans (Figure 8).

Hyperlipidemia can be the cause of lipemia retinalis due to elevated triglycerides in the retinal and choroidal circulation.¹⁹⁰

Lipemia retinalis usually improves with a reduction in fat intake and other therapies aimed at reducing triglycerides.¹⁹¹ Patients should be advised to lower their intake of egg yolks, whole-milk dairy products, and red meat, and substitute fruits, vegetables, and whole-grain food products. Coconut oil, palm oil, and hydrogenated vegetable oils should be replaced in cooking with olive oil or non-hydrogenated vegetable oils.¹



Figure 7: Many studies demonstrated that dietary interventions with vegetables, fruits, wholegrain bread, eggs, chicken, fish, milk and breakfast cereals were related to an increased folate intake and inversely associated with serum homocysteine levels; thus might potentially contribute to the effort of lowering homocysteine levels on ocular vasculopathic patients.



Figure 8: Foods that are rich in iron include beef, veal, fish, eggs, soya bean, broccoli and green beans.

Conclusion

Currently, evidence-based data on the role of nutritional factors on retinal disease are relatively limited. Results of the different studies are often inconsistent and precise nutritional recommendations on retinal diseases are not easy to be given in an absolute way.

Regarding AMD there is some evidence that patients with moderate AMD may benefit from a high-dose supplementation of a combination of vitamin C, vitamin E, β -carotene, zinc and copper in the dosages proposed by the AREDS trial and may be considered in

some cases. Additionally lutein, zeaxanthin and omega-3FAs may have a beneficial effect on AMD but their role has to be further determined. On the other hand, actually there is no evidence from randomized trials that nutritional elements may help healthy people to prevent or delay the onset of AMD and consequently no specific dietary patterns or nutritional supplements are currently recommended.

Further trials are warranted in order to clarify the role of nutritional elements on AMD. The results of several ongoing studies such as AREDS II are awaited with interest.



Considering patients presenting diabetic retinopathy a tight glycemic control is essential. Consequently, several nutritional patterns can adequately contribute to glycemic control and are currently highly recommended in these patients. In addition a low-fat diet is suggested. The role of specific micronutrients supplements, like antioxidants, on diabetic retinopathy although promising has yet to be further elucidated and is not currently recommended.

Regarding retinal vascular diseases although there are some indications that nutritional factors may play a role to their pathogenesis actually there is not enough evidence based data to recommend specific dietary patterns or nutritional supplements. Further studies are needed to clarify these associations.

Finally, one should consider that even if dietary recommendations regarding retinal diseases cannot be given a healthy diet, rich in green, leafy vegetables and fish, avoidance of high fat diets especially rich in saturated, monounsaturated, polyunsaturated, trans-unsaturated fats and linolenic acid is more probably beneficiary than harmful.

In conclusion, nutrition may have potentially important implications in the prevention and treatment of retinal diseases and its role has to be further clarified.

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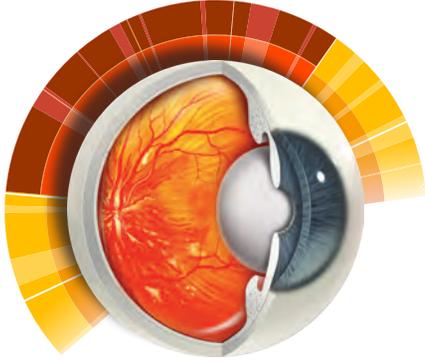
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Advances in Vitreoretinal Surgery

STEVE CHARLES, MD

During the last century, ophthalmology has been exploring new horizons both in the diagnosis and treatment of different pathologies, particularly in vitreoretinal surgery. These advances have been achieved mostly due to a better understanding of the various diseases as well as to the technological upgrades in the instruments utilized for vitreoretinal surgery.

Small Incision Vitrectomy Surgery

In recent years, vitrectomy surgery has seen major advancements in technology, quality and safety. The advent of the 25 gauge vitrectomy has enabled both surgical outcomes and shorter, more comfortable recovery for patients.

Microincision vitrectomy surgery (MIVS) is one of the most significant innovations in vitreous surgery since posterior vitrectomy was developed by Robert Machemer, MD, in the 1970. MIVS is defined as a combination of 25- or 23-gauge instrumentation and a transconjunctival sutureless procedure. The indication of MIVS was limited to macular surgery for several years after its introduction because of several disadvantages, including flexible instruments, lower aspiration rate, and insufficient illumination. The stiffness of instruments, cutting rates, and aspiration rates have been improved and the introduction of brighter light sources, such as xenon lamps, has improved illumination. As a result of these improvements, the indications for MIVS have expanded to include complicated cases with proliferative diabetic retinopathy and PVR (Figure 1).

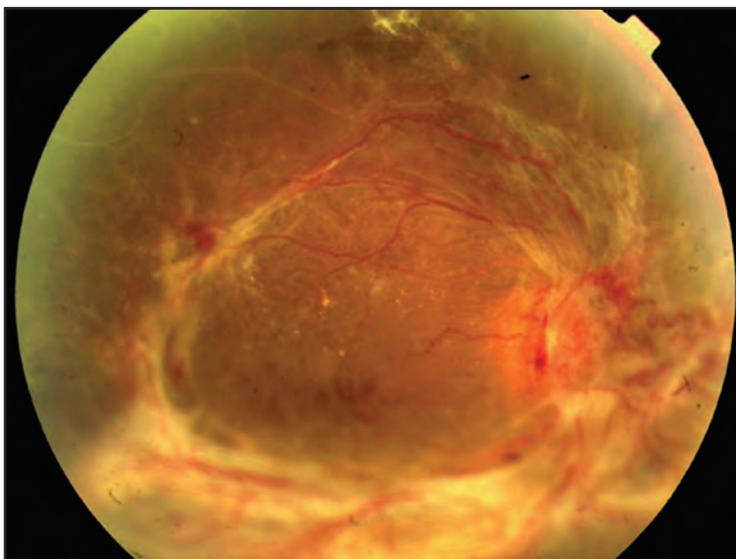


Figure 1. As retinal blood vessels become affected and close off in diabetic retinopathy due to the cumulative effects of diabetes, the peripheral portions of the retinal circulation begin to close down causing the retina to become ischemic. This process seems to be the first step in the development of proliferative diabetic retinopathy. Presumably, the ischemic retina releases a chemical growth factor which leads to the development of new abnormal blood vessels (neovascularization).

Improvements to instrumentation and illumination have also influenced surgical techniques. A small-gauge vitreous cutter on which the port is positioned closer to the tip allows for epiretinal membrane delamination.

Microincision vitrectomy surgery (MIVS) with 25- or 23-gauge instrumentation is undoubtedly one of the most impressive evolutions in the surgical retina field of the past three decades.^{1,2} Similar to the trend toward minimally invasive intervention in phacoemulsification for cataract surgery, smaller incisions in vitrectomy without peritomy and suturing have the potential to facilitate early visual recovery, diminish ocular surface irregularities, and decrease patient discomfort,

operating time, postoperative inflammation, and surgically-induced astigmatism. Therefore, MIVS is also known as “minimally-invasive” vitrectomy surgery. In contrast to the above-described benefits of MIVS, however, wound-sealing-related complications, such as hypotony, choroidal detachment, and a higher incidence of endophthalmitis, are major concerns of small-gauge vitreous surgery.

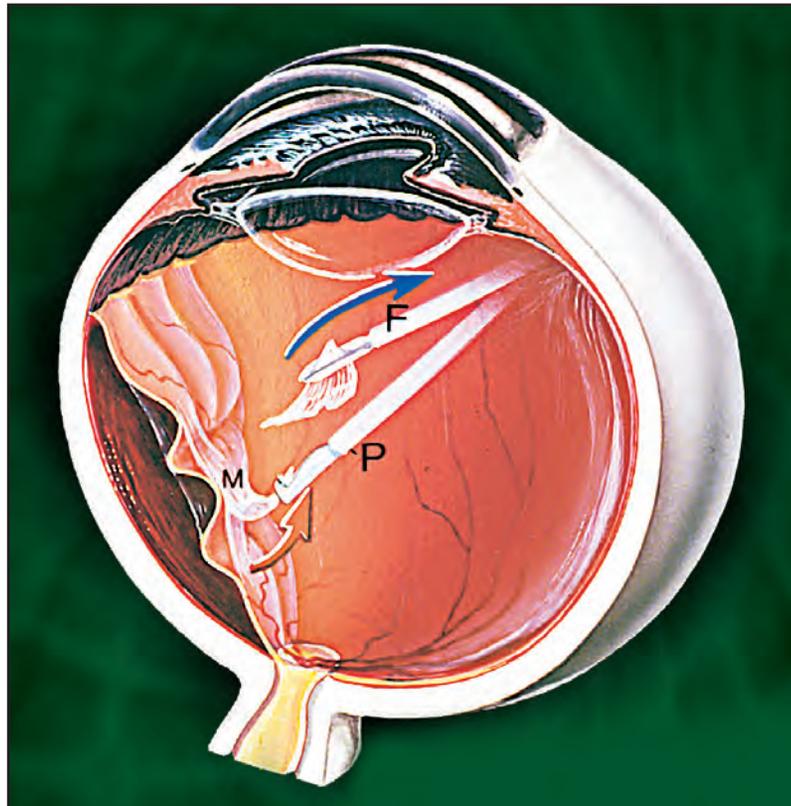
The transconjunctival 25-gauge system is another well-employed MIVS system. Although reduced illumination and cutting efficiency were concerns with 25-gauge early on, brighter light sources, such as xenon (Accurus High Brightness Illuminator, Alcon Laboratories Inc., Fort Worth, TX;) and the Constellation Vision System have addressed these concerns.



The 25-gauge vitreous cutter on the Accurus (Alcon Laboratories, Inc.) is highly efficient and is capable of 2,500 cpm. The high cutting rate and a port closer to the tip of the cutter have allowed surgeons to use 23/25-gauge for more challenging cases such as diabetic traction retinal detachments.^{3,4} During diabetic vitrectomy, a smaller gauge

vitreous cutter can conformal cutter delamination and foldback delamination of epiretinal membranes (Figure 2). Recent improvements in this equipments and the creation of stiffer instruments via shortening the shaft length and increased availability of accessories, will further expand the surgical indications of 23/25-gauge MIVS in many countries.

Figure 2. Management Epiretinal Membranes (M). Those membranes are usually engaged with a membrane pic (P) and lifted away (red arrow) from the surface of the retina. Intraocular forceps (F) are then used to completely remove the membranes from the eye (blue arrow). (Art from Jaypee - Highlights Medical Publishers).





Alcon Constellation Vision System

The Constellation is the culmination of over three decades of evolutionary development of vitreous cutters and fluidics, new and improved tools, xenon illumination sources, phaco technology, new laser technology, systems integration, efficiency systems, and advanced user interface design. The author is the principle architect of the Alcon Constellation Vision System (Figure 3).

The VISC and RotoExtractor were single port, large incision, so-called full function, slow speed, rotary, electric cutters with as-

piration provided by a syringe operated by the assistant. The Berkley Bioengineering Ocutome 800, developed by Conor O'Malley, MD and Ralph Heinz was the first three-port, 20-gauge (0.89mm) system and had the first lightweight, pneumatic probe and surgeon foot pedal to control on-off aspiration; a major advance. Berkley Bioengineering subsequently was acquired by Coopervision and Coopervision was later acquired by Alcon Laboratories. The Coopervision Ocutome 8000, developed by Carl Wang, his engineering team, and myself, had the first linear suction (now used on all vitrectomy and phaco machines), an integrated light source, and a connected fragmenter. The MidLabs MVS system, developed by Carl Wang and I, had



Figure 3: Constellation Vitrectomy System.



the first disposable pneumatic cutter; a crucial improvement over reusable cutters with low performance cutting. After the original MidLabs was acquired by Alcon Laboratories I started InnoVision and began development of the OCM. The OCM had a dual actuation InnoVit cutter with limited angle rotary cutting at 1500 cuts/minute, linear diathermy, tool ID, an articulated arm with integrated tubing management, servo controlled IOP, a graphical user interface with soft keys, integrated xenon illuminator, integrated fragmenter, auto-gas mixing, auto fluid-air exchange valving, and power scissors. The InnoVision OCM technology was never commercialized

and was later acquired by Alcon Laboratories and I became a consultant for Alcon. Many of the OCM concepts were improved upon and incorporated into the highly successful Accurus system which included an advanced graphical user interface with soft keys and global functions, VGFI (vented gas forced infusion), integrated fragmenter, silicone injector (VFC), and a halogen light source. 25-gauge and later 23-gauge tools were developed for the Accurus platform and are now in their third generation (Figure 4). A non-integrated EyeLite 532nm diode pumped laser and later a non-integrated xenon source were developed to use with the Accurus system.

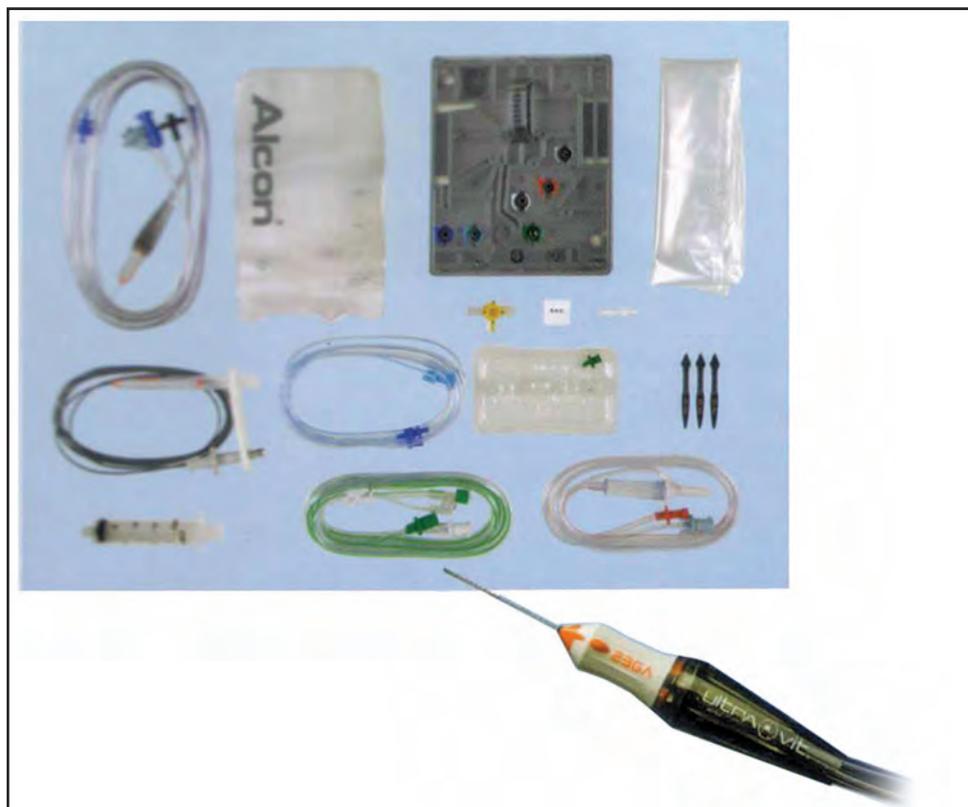


Figure 4: 23-Gauge package for non-sutured vitrectomy.



The Constellation incorporates new, improved implementations of all the concepts incorporated in the OCM as well as the Accurus and adds many new capabilities. The vitreous cutter is the pivotal component of any vitreoretinal surgery system; the Constellation UltraVit cutter utilizes dual pneumatic actuation (no spring return axial cutter) like the InnoVit and currently operates at 5000 cuts/minute. Because it is diaphragm driven it eliminates the friction of the InnoVit piston, provides the familiar axial cutter format, and scales better to 23, 25 and even 27 gauge form factors. The cutter is driven using a proprietary variable duty cycle technology dependent on the dual actuation system. Variable duty cycle control enables use of a biased closed approach to produce increased port-based flow limiting when working in close proximity to the retina; so-called vitreous shaving. Alternatively, port-based flow limiting can be decreased by using a biased open approach enabling greater flow rates when doing core vitrectomy. The aspiration system has a low latency response time to a foot pedal command for vacuum decrease or increase because of a new, triple proportional valve aspiration system and cassette design. Sensor-based, fast response, digital flow control and flow limiting facilitate working safely near the retinal surface. The aspiration system provides continuous linear (proportional) reflux as well as micro-reflux for all aspiration tools enabled by routing the infusion system through the vacuum cassette.

The Constellation utilizes a real-time operating system and distributed processor architecture to ensure reliability as well as

2X faster response time than the Accurus. It has a switched Ethernet architecture with 42 printed circuit boards, a Pentium CPU, five microprocessors, many FPGAs, and uses over 600,000 lines of code. The electronics have power back up for situations such as the cord being pulled out or power failure in the OR to facilitate rapid resumption of surgery.

Integrated pressurized infusion using a two chamber system and servo control of the intraocular pressure (IOP) is unique to the Constellation and is especially valuable in high flow scenarios such as removal of dislocated dense lens fragments using the fragmenter with 23 or 25G infusion. IOP compensation is accomplished by sensing fluidic resistance in the infusion circuit during push priming by sensing flow and pressure. The infusion pressure is automatically increased as flow increases during surgery to control the IOP within ± 2 mmHg. IOP compensation will reduce sudden IOP decrease and resultant bleeding after dense epiretinal membrane deforms through the cutter port. It is likely that IOP compensation will enable use of lower average infusion pressures. The infusion system has automatic bottle out warning and enables changing bottle with no interruption in fluid flow or bubbles.

The Constellation can be configured with one or two, dual port xenon illumination sources to facilitate use of illuminated tools, chandeliers, and Torpedoes. The new xenon illuminator design is more efficient and produces 2X longer, 400 hour lamp life. The author typically uses 12-16% intensity settings



because the efficient xenon source and fiber coupling technology. The xenon optical system produces greater than 25 lumens using 23G and 25G fibers at 200 hrs. Radio frequency identification (RFID) connectors on the illumination tools automatically adjust the initial xenon source intensity depending on specific tool characteristics: light throughput, typical working distance, and divergence angle. This set-point is 8-10 lumens which is the optimal light intensity for all tools in 20, 23, and 25G. The surgeon can increase illumination, if needed, to the maximum FDA allowed output.

RFID in the tool connectors activates parameter and mode setup decreasing setup time as well as workload and training requirements for the circulator. RFID also activates a new time saving, push prime system for the vitreous cutter and any connected extrusion tools. A sterile articulated arm incorporating a tubing management system enables priming and testing of all infusion and aspiration components before the patient is anesthetized, prepped, and draped; significantly decreasing setup time and eliminating the need for a Mayo stand to support the tubing and surgical drape. Embedded wizards and digital instructional video facilitate faster setup especially when using less experienced personnel.

The Constellation is usually configured with an embedded PurePoint 532nm laser. The PurePoint laser is a novel, advanced, thin-disk 532 nm solid state laser. The thin-disk laser engine reduces thermal lensing, which are changes in the index of refraction

of the Nd Vanadate lasing medium as it heats up. The thin-disk design produces a more constant laser output especially with higher powers and firing rates because of thermal stability. The lithium triborate frequency upconversion crystal (1064 nm to 532 nm), thermal electric cooler, and all optomechanical components are solder mounted in a fixed, mechanically and thermally stable position. A separate foot pedal controls laser power and standby/ready/standby control with voice verification eliminating dependence on the circulator. The Constellation graphical user interface eliminates the need for a separate display and controls.

An Auto Infusion Valve replaces the stop-cock used for fluid-air exchange eliminating delay while air travels through 84 inches of tubing and bubbles. The auto infusion valve can be controlled by the surgeon's foot pedal or the scrub tech using the Constellation sterile graphical user interface.

Auto Gas Syringe Fill system enables filling the syringe from attached tanks of SF₆ and C₃F₈ reduces gas wastage, ensures sterility, and eliminates the need for the circulator to assist the scrub tech. A software applet calculates how much air to add to the gas to produce the surgeon's desired concentration of gas in air.

The VFC power silicone/perfluorocarbon liquid injector supports simultaneous aspiration and has RFID to automatically configure the Constellation mode.



Advanced phaco technology including Ozil torsional phaco is embedded in the Constellation to support both combined phacoemulsification-vitreotomy (phaco-vit) procedures as well as phaco only procedures. The Constellation, digital, fast, non-pulsatile flow control is superior to conventional peristaltic pump technology for phaco procedures.

The Constellation has proportional control of new, higher frequency, 1.5 MHz, sinusoidal diathermy system producing 10 watts maximum. Higher frequency diathermy produces a more focused lesion possibly reducing retinal damage. Proportional control eliminates the need for the nurse or scrub technician to adjust the power and facilitates optimal intensity.

Power forceps with linear (proportional) control as well as power scissors with single-cut and multi-cut modes support disposable Alcon Grieshaber disposable DSP ILM and end-grasping forceps as well as vertical and curved scissors tips. Bimanual surgery (is supported by single pedal linear control of power forceps to grasp and stabilize epiretinal during the initial segment of pedal travel followed by control of the power scissors with further depression of the pedal.

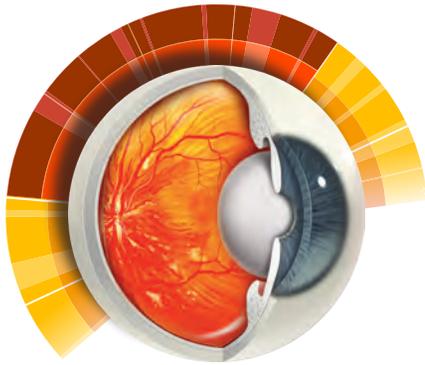
Turnover time is greatly reduced because RFID on all tools initiates automated push-

prime, testing and setup. The articulated arm system enables sterile setup and testing prior to or in parallel with. RFID and a barcode reader identify all consumables without RFID generate consumable use data for a wireless printer or LAN based connection. Surgical parameters and steps, laser log, and consumable use reports are generated automatically and printed on wireless printer for inventory control, cost accounting, billing, analysis, or incorporation into an operative note.

In summary, the Alcon Constellation Vision System addresses all the needs of the vitreoretinal and cataract surgeon using the most advanced surgical and efficiency technologies.

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Ocular Gene Therapy: An Evaluation of rAAV-mediated Gene Therapy Interventions for the Treatment of Ocular Disease

KAMOLIKA ROY, MD
LINDA STEIN, MD
SHALES KAUSHAL, MD

Abstract

Both gene replacement therapy and alteration of host gene expression are playing increasingly important roles in the treatment of ocular diseases. Ocular gene therapy may provide alternatives to current treatments for eye diseases that are either greatly invasive and thus run the risk of complications, that offer only short-term relief from disease symptoms, or that are unable to directly treat vision loss. The recent success of three separate Phase I clinical trials investigating a gene therapy intervention for the treatment of the retinal degenerative disorder Leber's congenital amaurosis (LCA) have unveiled the therapeutic

potential of gene therapy. Preliminary results have demonstrated ocular gene transfer, using non-pathogenic recombinant adeno-associated viral (rAAV) vectors specifically, to be a safe, effective, and long-term treatment for LCA, a previously untreatable disorder. Non-pathogenic rAAV vectors offer the potential for long-term treatment. Many of the genes implicated in human ocular diseases have been identified, and animal models for such diseases have been developed, which has greatly facilitated the application of experimental rAAV-mediated gene therapy. This review highlights the key features of rAAV-mediated gene therapy that make it the most suitable gene therapy treatment approach for ocular diseases. Furthermore, it summarizes



the current progress of rAAV-mediated gene therapy interventions/applications for a wide variety of ophthalmologic disorders.

Ocular Gene Therapy: An Introduction

Visual function is directly dependent on the health of the numerous tissues that comprise the eye, and these tissues are often implicated in a variety of ocular diseases. Disease can affect external, anterior structures of the eye, including the cornea and lens, as well as the innermost regions of the retina and the optic nerve. Many of the inherited dystrophies and acquired disorders that affect ocular structures have been demonstrated to be amenable to rAAV-mediated gene therapy in pre-clinical models. Some examples of diseases treatable with rAAV-mediated gene therapy include neovascularization of the retina, choroid, and cornea, as well as the maternally inherited disorder primarily affecting the optic nerve, known as Leber's hereditary optic neuropathy. The inherent structural features of the eye also make it well-suited as a target organ for rAAV-mediated gene therapy. Both the small size and compartmentalized structure of the eye reduce the rAAV vector-encoded gene necessary to obtain a substantial therapeutic effect, and confine rAAV vector delivery to only the affected area of the eye. Additionally, the accessibility of the eye facilitates multiple administration routes for therapeutic rAAV vectors and allows diverse types of ocular cells to be transduced.¹

The development of rAAV vectors has made it possible for gene therapy to overcome the challenges of efficiency and prolonged gene transduction; rAAV vectors have been shown to sustain gene transduction for up to year in a wide array of cell types. Also, rAAV vectors are particularly well-suited for gene therapy interventions of the eye as they are the only viral vectors able to efficiently transduce both photoreceptor and RPE cells and can also transfect Müller and retinal ganglion cells.^{2,3} In addition, rAAV vectors can target specific ocular cell types, which both increases transduction efficiency as well as decreases the chances for targeting cells unaffected by disease or damage. These characteristics of rAAV vectors further demonstrate the potential that rAAV-mediated gene therapy holds for the treatment of ocular diseases.

A major limitation to rAAV-mediated gene therapy is the small packaging capacity of the rAAV vector,³ with the transgene to be packaged often exceeding the vector's 5kb capacity. However, the recent development of hybrid rAAV vectors has expanded the genomic size limitation to fit transgenes up to 9kb. This will be discussed in the context of various specific rAAV vector and ocular disease applications. Additionally, the slow onset of transgene expression following rAAV-mediated transduction constitutes another limitation of this gene therapy vector. The challenge presented by slow onset of transgene expression is most pronounced in treatment of early onset disorders, such as rapidly degenerating retinal dystrophies.



Despite such limitations, rAAV-mediated gene therapy offers a multitude of treatment options for ocular diseases. The recent discovery of novel rAAV vector serotypes has given way to the development of the aforementioned hybrid vectors. The novel rAAV serotypes of hybrid vectors modulate the cellular tropism of the vector, increasing both its specificity and efficacy. rAAV-mediated gene therapy in the eye also has numerous administration routes; both non-invasive and invasive delivery methods can be used depending on the ocular tissue target.

The prospects for rAAV-mediated gene therapy to treat various ocular diseases continue to be studied in numerous *in vitro*, *in vivo*, and *ex vivo* experimental models. Ocular disease models have been created *in vivo* in rats, monkeys, mice, and dogs, among others. Efficient rAAV-mediated gene transduction of corneal cells has been demonstrated *in vivo* in animal models, as well as in *ex vivo* organ cultures. The extensive pre-clinical studies of rAAV-mediated gene therapy applications for ocular diseases have culminated in the first successful ocular gene therapy clinical trial. Three different Phase I clinical trials were conducted to investigate the therapeutic potential of rAAV-mediated gene therapy in Leber's congenital amaurosis (LCA). Thus far, results from all three clinical trials have proven quite promising, as some of the patients enrolled in the study are experiencing marked improvements in their vision. As data continues to be collected from the LCA clinical trials, advancements in pre-clinical

studies of rAAV-mediated gene therapy for other ocular diseases persist. Although ocular gene therapy with rAAV vectors is only in its initial stages, the future looks bright for the use of rAAV-mediated gene therapy as a long-term therapeutic for the treatment of ophthalmologic disorders.

rAAV-Mediated Ocular Gene Transfer

Ocular function is entirely dependent upon many internal specialized structures, which capture an image in the form of visible light and transduce the light into neural signals. Specifically, the photoreceptor cells of the retina transduce photons into electrical impulses that are transmitted to the brain via the optic nerve. A variety of ocular tissues that contribute to visual function may be involved in inherited and acquired diseases, previously untreatable, for which ocular rAAV-mediated gene therapy approaches are being developed.

The rAAV vector is a non-pathogenic, human parvovirus with a linear, single-stranded DNA genome. The vector construct consists of two reading frames, *rep* and *cap*, enclosed between two symmetric T-shaped palindromic terminal sequences called inverted terminal repeats (ITRs). To generate the non-replicating rAAV vector, the *rep* and *cap* reading frames are deleted from the genome and the therapeutic gene is inserted between the ITRs.⁴



The rAAV vector does present some limitations, given its small packaging capacity of 5kb and a slow onset of transgene expression following transduction.³ These limitations, however, are far outweighed by the efficacy of rAAV vector-mediated gene therapy as a treatment for ocular diseases. Low immunogenicity is among the many optimal features of the rAAV vector that allow it to sustain transgene expression for up to a year and induce little to no ocular inflammation (unlike adenoviral vectors); present minimal risk of insertional oncogenesis (unlike retroviral vectors); and transduce a wide array of ocular cell types (unlike lentiviral vectors). rAAV vectors are the only viral vectors able to efficiently transduce both photoreceptor and retinal pigment epithelial cells, and they can also transfect Müller and retinal ganglion cells.^{2,3}

In addition, structural features of the eye make it well-suited as a target organ for rAAV-mediated gene therapy. The small size of the mammalian eye reduces the amount of vector and/or gene needed to observe a therapeutic effect, and its highly compartmentalized structure facilitates accurate delivery of the therapeutic vector. Also the blood-retina barrier of the eye constrains the rAAV vector to the site of delivery, which prevents any systemic leakage of the vector. In addition the transparency of the external layers of the eye facilitates noninvasive imaging of ocular tissues *in vivo*.^{5,1}

Specificity of rAAV-Mediated Ocular Gene Therapy

The tropism rAAV vectors demonstrate towards specific ocular tissues is derived from the rAAV serotype of the vector as well as the site of vector and/or gene delivery within the highly compartmentalized anatomy of the eye.⁶ The rAAV serotype dictates the expression kinetics of a given rAAV vector; a variety of rAAV vectors are available because of the numerous rAAV serotypes that exist. rAAV serotypes are differentiated based on the structural capsid protein sequences encoded within the cap gene of the rAAV vector construct. Numerous hybrid vectors containing novel rAAV serotypes have been developed to modulate cellular tropism of an rAAV vector to increase its efficacy. The pseudo typing strategy used to design hybrid vectors was first developed with the rAAV2 serotype, the most abundant serotype in the human population, which has long been used in designing rAAV vectors and has been studied extensively.⁵ To generate hybrid vectors using the AAV2 serotype, an expression cassette containing the AAV2 genome (including the therapeutic gene bordered by the ITRs on either side) was packaged into the capsid protein of another serotype. The resulting hybrid vectors have demonstrated varied kinetics of transgene expression and improved tropism for a broad range of cell types because of their novel serotypes. The rapid-onset rAAV-2/1, -2/5, and -5/5 vectors



can demonstrate transgene expression 3 to 4 days after vector delivery. The transgene expression for rAAV-2/2 vector has a delayed onset, reaching a stable level of expression 2 to 4 months after vector delivery.⁶ Hybrid vectors have also been shown to transduce

a wide array of ocular tissues, including retinal pigment epithelial cells; corneal cells; photoreceptors cells; the bipolar, amacrine, and Müller cells of the inner retina; retinal ganglions cells; and cells of the anterior ocular structures (Figure 1; Table 1).

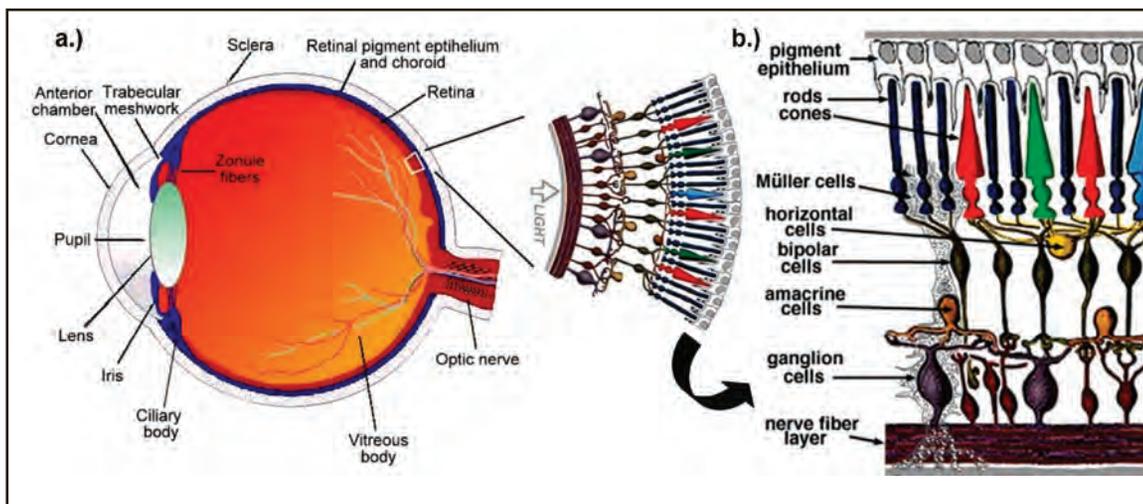


Figure 1: Structure and Function of the Eye. (a) Vertical sagittal section of the adult human eye, and schematic of human peripheral retina.(b) Schematic enlargement of retinal cells. Source: Webvision: (a) Gross Anatomy of the Eye, Fig. 6, <http://webvision.med.utah.edu/anatomy.html> (modified); (a) and (b) Simple Anatomy of the Retina, Fig. 10 and Fig. 1.1, respectively, <http://webvision.med.utah.edu/sretina.html> (modified).



Table 1. Ocular Cell Tropism of Hybrid rAAV2 Vectors after Specific Vector Administration Route

rAAV serotype	Ocular cells transduced by subretinal injection	Ocular cells transduced by intravitreal injection	Ocular cells transduced by topical application
rAAV-2/1	RPE, Müller-(mouse); PR, RGC-(rat)	RPE, RGC (rat)	Cornea (rabbit, human)
rAAV -2/2	RGC, RPE, PR(mouse)	RGC, optic nerve (mouse, rat); Müller, trabecular meshwork (mouse)	Cornea (rabbit, human)
rAAV -2/3	-	PR, RGC (rat)	-
rAAV -2/4	-	RPE (mouse, rat), RGC, amacrine, Müller (rat)	-
rAAV -2/5	RPE, PR, Müller (mouse); RGC (rat)	PR, RGC (rat)	Cornea (rabbit)
rAAV -2/6	-	Amacrine, bipolar, Müller, RGC, optic nerve (rat)	-
rAAV -2/7	RPE, PR (mouse)	Trabecular meshwork, iris, cornea, lens (mouse)	Cornea (rabbit)
rAAV -2/8	RGC, PR, RPE, Müller (mouse)	Trabecular meshwork, Müller, iris, cornea, lens-(mouse); RGC (mouse, rat)	Cornea (rabbit, human)
rAAV -2/9	RPE, PR, Müller (mouse),	Müller, iris, cornea, lens (mouse)	-

Abbreviations: RPE, retinal pigment epithelium; RGC, retinal ganglion cells; PR, photoreceptors.^{7,8,9}



Routes of Administration

The route through which rAAV vector will be delivered depends on which of the numerous ocular cell types it will transduce. The various administration routes described here are illustrated below in Figure 2. When rAAV vectors are used to transduce photoreceptors and retinal pigment epithelial cells, which are predominantly implicated in inherited retinal degenerative disorders, the vectors are administered via subretinal injection. Since the vector suspension is delivered between the retina and the retinal pigment epithelium, subretinal injections cause temporary separation of the retinal layers.⁶ Figure 3 shows a subretinal injection of rAAV2-CB-hRPE65 in a LCA clinical trial patient. When rAAV-mediated gene therapy is used to transduce retinal ganglion cells and other cells of the inner retina that are com-

monly implicated in optic neuropathies such as optic neuritis and glaucoma, the vector is injected intravitreally.⁴ Intravitreal injection has been shown to reach the photoreceptor cells of the outer retina and could therefore provide a less invasive delivery alternative to subretinal injection. Furthermore, intravitreal injection allows for a larger vector dosage to be delivered; repeated injections within the vitreous body; and vector delivery in conjunction with a pharmacological agent.⁹ Topical application is a common route of administration for therapeutic vectors used to treat diseases involving the conjunctival and corneal epithelia.^{10,11} Periocular injection is the route of administration for vectors treating neovascular and corneal diseases.^{12,1} Delivery of rAAV vectors by anterior chamber injection has been used *in vivo* to transduce rabbit corneal endothelium as a model for disorders of the corneal endothelium.¹¹

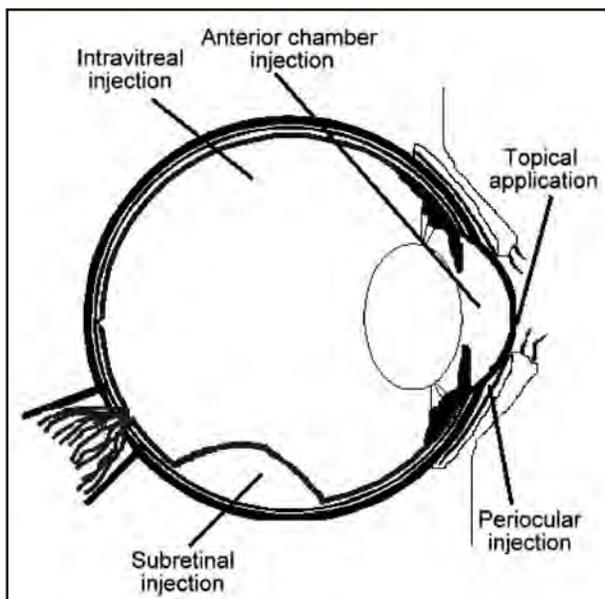


Figure 2: Administration routes for rAAV vector delivery.

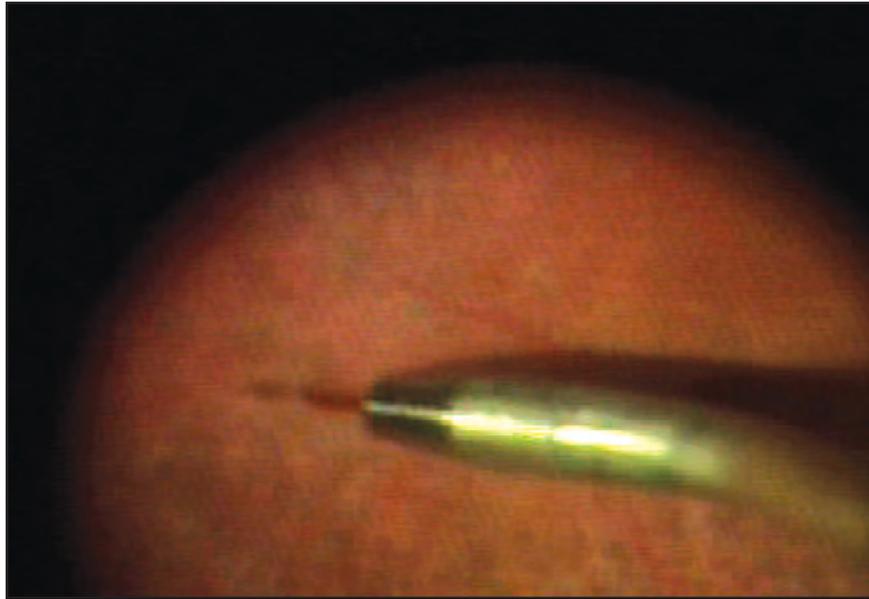


Figure 3: Administration of rAAV2-CB-hRPE65 by subretinal injection to LCA clinical trial patient.

Efficiency of rAAV-mediated Ocular Gene Therapy

For target organs other than the eye, transient gene transfer is a disadvantage of rAAV-mediated gene therapy in dividing cells. However, this drawback is largely overcome when the target organ is the eye, since it is composed of an array of primarily non-dividing cells. As a non-integrating vector, the rAAV vector DNA does not integrate into the host genome, thus the duration of transgene expression is not affected, making rAAV vector transduction in the eye more efficient. The efficiency of ocular vector transduction is dependent upon a number of factors, including the routes of vector administration discussed above and the promoter sequence

of the vector, which provides the impetus for transgene expression.² Furthermore, efficiency of rAAV vector transduction can be enhanced. In 2008, Zhong *et al.* demonstrated the high-efficiency transduction of rAAV-2 vectors at lower doses. Through site-directed mutagenesis of the surface-exposed tyrosine residues on the capsid proteins of rAAV-2 vectors, the vectors were able to avoid phosphorylation. Subsequently, the tyrosine-mutant rAAV-2 vectors escaped ubiquitination and thereby circumvented proteasome-mediated degradation. These results indicated an increase in transduction efficiency of the tyrosine-mutant rAAV-2 vectors, as well as improved intracellular trafficking to the nucleus.¹³ Table 2 summarizes rAAV-mediated gene therapies for ocular diseases.



Table 2. rAAV-mediated Treatment for Ocular Diseases

Disease Name	Affected Tissue	Inheritance Pattern	Disease Presentation	Gene Amenable to rAAV-mediated Gene Therapy	Challenges/Expected Outcomes with rAAV-
<i>Inherited Ocular Disorders</i>					
Leber Congenital Amaurosis	Retina	Autosomal recessive	Appears at birth, or no pupillary responses	Mutations in <i>RPE65</i> gene cause deficiency RPE65 enzyme, (which converts of all trans-retinoids to 11-cis retinoids); visual cycle is interrupted and lack of visual pigment results; <i>LRAT, RDH12, RPGRIP</i>	Gene therapy has been a successful for mutation in LRAT and in RPE65 with which it's improved vision by restoration of absent photoreceptor function; gene therapy not evaluated for RDH12 mutations
Autosomal Dominant Retinitis Pigmentosa	Retina	Autosomal dominant	Early-onset retinal dystrophy, tunnel vision preceded by night-blindness	Mutation in rhodopsin <i>RHO</i> gene (RHO-adRP)	rAAV-mediated RNAi suppression of Pro347Ser mutant <i>RHO</i> in conjunction with endogenous <i>RHO</i> gene expression
Autosomal Recessive Retinitis Pigmentosa	Retina	Autosomal recessive	Early-onset retinal dystrophy, tunnel vision preceded by night-blindness	Mutation in genes encoding phototransduction proteins and photoreceptor outer segment regulation PDE6B, MERTK, respectively.	Rapid degeneration of photoreceptors proves challenging for effective rescue by gene replacement therapy; rAAV5 mediated gene replacement of hypomorphic PDE6B allele injected subretinally in rd10 mouse model with partial PDE6B deficiency demonstrated prolonged photoreceptor survival and improved vision
X-linked Retinitis Pigmentosa	Retina	X-linked recessive	Early-onset retinal dystrophy, tunnel vision preceded by night-blindness	Mutation in <i>RPGR</i> gene	Multiple protein isoforms of RPGR and slower degeneration of photoreceptors in Rprg-deficient mouse model complicates assessment of efficacy of gene replacement therapy
Achromatopsia	Retina	Autosomal recessive	Early-onset retinal dystrophy, lack of cone function resulting in color blindness, reduced central vision and photophobia	Mutations in <i>GNAT2</i> , encodes component of cone phototransduction cascade and <i>CNGB3</i> , encodes β subunit of cone cyclic nucleotide-gated cation channel	Success of gene therapy to improve cone function may depend on age at which patient receives treatment, but AAV2/5 mediated gene replacement in a dog model has been successful
Stargardt Disease (Juvenile Macular Degeneration)	Retina	Autosomal recessive	Early-onset retinal dystrophy, characterized by alterations of the peripheral retina, and subretinal deposition of lipofuscin-like material	Mutations in <i>ABCA4</i> gene cause abnormal fxn of ABCA4 transporter protein (which translocates N-retinylidene-PE from the lumen of the disc to the photoreceptor cytoplasm); absence of fxnl ABCA4 allows N-retinylidene-PE to accumulate in lumen	AAV2/5 mediated gene therapy reduced lipofuscin content and improved retinal morphology and function in mouse model
Usher Syndrome	Retina	Autosomal recessive	Rare retinal dystrophy affecting proteins ciliary function and characterized by deafness and gradual vision loss from RP	<i>MYO7A</i> gene is expressed in many cell types including RPE and photoreceptors	AAV2/5 mediated gene replacement could be successful to treat MYO7A-deficiency in Usher1B
Bardet Biedl Syndrome	Retina	Autosomal recessive	Rare retinal dystrophy affecting proteins ciliary function causing development of low vision/ blindness from RP	Mutated gene causes impairment of photoreceptor transport mechanism in the retina	Since gene mutations have syndromic defects, and therefore widespread pathologies, developing gene therapy more of a challenge



Table 2. rAAV-mediated Treatment for Ocular Diseases (continued)

Disease Name	Affected Tissue	Inheritance Pattern	Disease Presentation	Gene Amenable to rAAV-mediated Gene Therapy	Challenges/Expected Outcomes with rAAV-mediated Gene Therapy
<i>Inherited Ocular Disorders</i>					
Juvenile Retinoschisis	Retina	X-linked recessive	Early-onset retinal disease where retina separates into several layers and may detach	Mutation in <i>RS1</i> gene encodes for retinoschisin, a protein integral to retina for cellular adhesion and tissue stability	AAV5 mediated gene therapy improved retinal function in mouse model
Leber's Hereditary Optic Neuropathy	Optic Nerve	Mitochondrial	Optic neuropathy causing loss of central vision	Mutation in ND4 subunit gene (G->A transition at nucleotide 11778)	Use allotopic expression to express nuclear-encoded version of mitochondrial ND4 gene in genome mitochondrial gene
Primary open-angle glaucoma	Retina & Optic Nerve	Autosomal dominant	Disorder causing extensive optic nerve damage and blindness caused by retinal vein occlusion induced-elevated intraocular pressure	Mutation in <i>MYOC</i> gene that encodes for myocilin protein	None found
Multiple Sclerosis	Optic Nerve	Multifactorial	Optic neuritis resulting in loss of visual function after multiple episode of optic neuritis	Demyelination of oligodendrocytes in optic nerve by free radicals	AAV-catalase (free radical scavenger) mediate therapy targets oligodendrocytes to suppress demyelination of them
Red-green Color Blindness	Retina	X-linked recessive	Cone dystrophy resulting in inability to distinguish red from green	Congenital absence of L-opsin gene, which encodes L-photopigment	Correction of dichromatic, red-green color blindness following rAAV2/5-mediated gene replacement of L-opsin gene in adult male squirrel monkeys
<i>Acquired Ocular Disorders</i>					
Glaucoma (Acquired)	Retina, Trabecular meshwork, Optic Nerve	-	Optic neuropathy resulting in neuronal damage from long-term elevated intraocular pressure	Increased ocular pressure causes BDNF deprivation of RGCs, which are trophically dependent of BDNF	Gene therapy of glaucoma focuses on slowing the rate of RGC death by RGC transfection with AAV-BDNF mediated therapy & inhibition of RGC apoptosis with AAV-BIRC4 (caspase inhibitor) mediated therapy
Age-related macular degeneration	Retinal pigmented epithelium and choroid	-	Wet form caused by choroidal neovascularization where blood and other fluids leak into macula from these new vessels;	Use of anti-angiogenic, neurotrophic protein to regulate vasculature development in the choroid	Reduction in development of choroidal neovascularization as well as the regression of already developed CNV in a murine model following rAAV-PEDF mediated transgene expression
Diabetic retinopathy	Retina	-	Retinal neovascularization due to long-term diabetes causes scotomas and blurred vision that can lead to blindness	Use of anti-angiogenic factors to regulate neovascularization of the retina	Reduction in retinal neovascularization. After rAAV-mediated expression of a soluble form of the Flt-1 (sFlt-1) receptor in inhibiting the angiogenic action of VEGF
Corneal angiogenesis	Cornea	-	Arises from neovascularization of the cornea, an otherwise avascular ocular tissue	Use of anti-angiogenic factors, i.e. angiostatin to regulate corneal angiogenesis	Observed regression of corneal neovascularization and subsequent angiogenesis following rAAV-angiostatin mediated transgene expression in experimental alkali burn-induced corneal angiogenesis in rats



rAAV-Mediated Gene Therapy for Corneal Diseases

The cornea is a transparent tissue chiefly involved in protecting the structure and function of the eye. As the outermost ocular structure, the cornea protects the eye from any physical and pathogenic injury due to the external environment. The cornea also plays an immunoprotective role through its expression of inhibitors that prevent activation of pro-inflammatory factors, as well as through its secretion of cytokines. The protective function of the cornea is regulated by the five cellular layers that comprise the cornea, including the epithelium, Bowman's membrane, stroma, Descemet's membrane and endothelium. Direct accessibility of the corneal epithelium to the external environment facilitates more convenient vector delivery methods for gene therapy, such as non-invasive, topical administration; however, invasive vector delivery methods, including injection into the anterior chamber, have yielded greater transduction efficiencies.¹⁴ While gene therapy holds great potential in the treatment of inherited corneal endothelial diseases, as well as in the prevention of corneal allograft rejection,¹⁵ the most extensive research concerning rAAV-mediated gene therapy in the cornea has been conducted in experimental models of acquired corneal endothelial disorders.

Acquired Corneal Diseases

Ocular neovascularization is a threatening condition in all of the tissues of the

eye that it can affect, and particularly so in the avascular cornea. The transparent and immunoprotective nature of the cornea is compromised in corneal neovascularization, which can be induced by a wide variety of factors including inflammation, infection, degeneration, and by both direct trauma to the cornea and indirect trauma to the limbus structure that borders it. Treatment approaches focus on the regulation of corneal angiogenesis to counter the development of new blood vessels from pre-existing pathological vasculature. The homeostatic mechanism behind the regulation of corneal angiogenesis involves both pro- and anti-angiogenic factors, many of which have been used in conjunction with rAAV-mediated gene therapy approaches. Specifically, the rAAV-mediated gene transfer of angiogenesis inhibitors such as angiostatin and endostatin has been shown to reduce and even inhibit corneal neovascularization.^{12,16}

Recently, Cheng *et al.* observed a regression in corneal neovascularization due to experimental alkali burn-induced corneal angiogenesis in rats given a subconjunctival injection of rAAV-angiostatin. After establishing efficient rAAV-mediated transduction by GFP transgene expression, the experimental rats were divided into two groups and treated with either a blank rAAV control vector or a rAAV-angiostatin vector. In both cases, the viral vector was administered by subconjunctival injection three weeks prior to the induction of the alkali burn-induced corneal angiogenesis. Corneal neovascularization was observed one week after injury induction and subsequently quantified by calculating the area of marked neovascular engorgement. The prolonged exposure of



the limbal and conjunctival vasculature (the site at which corneal neovessels originate) to transgene expression was determined to account for the observed regression in corneal neovascularization of the rAAV-angiostatin treated group.¹²

The corneal endothelium has presented challenges for gene therapy in terms of both efficient and prolonged gene transduction, which rAAV-mediated gene transfer has been able to overcome. Until recently, however, *in vivo* regulation of transgene expression proved difficult even for rAAV-mediated gene therapy. In 2002, Tsai *et al.* demonstrated prominent transgene expression in the corneal endothelium *in vivo* when induced by inflammation. Following pre-treatment with the rAAV vector containing the *LacZ* reporter gene, inflammation was induced by intravitreal injection of lipopolysaccharide (LPS) in the ocular anterior chambers of New Zealand rabbits. A direct correlation was observed between transient ocular anterior segment inflammation induced by the lipopolysaccharide injection and increases in *LacZ* gene expression in the rabbit corneal endothelial cells. Results revealed a peak in inflammation one day after LPS injection; the inflammation concurrently activated transgene expression of *LacZ* in approximately 90% of corneal endothelial cells. Furthermore, a second LPS-injection, given 60 days after the first, elicited a dramatic reactivation of transgene expression to levels once again nearing 90% of endothelial cells, even after transgene expression diminished as inflammation subsided following the first LPS injection. This finding of increased transgene expression following transient LPS-induced inflammation has expanded the implications of rAAV-mediated gene therapy

for the treatment of other acquired corneal diseases including keratitis, anterior uveitis, and corneal graft rejection.¹⁵

In a more recent study by Tsai *et al.*, the effect of cell-specific and inducible-expression systems on the level and timing of transgene expression in the treatment of experimental uveitis was investigated. Uveitis is a recurrent, intraocular inflammatory condition that can severely compromise vision. In previous gene therapy studies investigating the therapeutic potential of interleukin-1 receptor antagonist (IL-1Ra) as a treatment for uveitis, the efficiency of intraocular gene transfer by the chosen vector delivery systems was limited. Therefore, Tsai *et al.* employed the use of the rAAV vector encoding IL-1Ra cDNA to elicit transgene expression in the eyes of New Zealand white rabbits. The rAAV-IL-1Ra vector, as well as a control vector encoding the *LacZ* reporter gene were administered intravitreally. The therapeutic potential of rAAV-IL-1Ra was assessed after induction of experimental uveitis by intravitreal injection of rAAV-IL-1 α at both 10- and 100-day timepoints following rAAV-IL-1Ra delivery. Using methods of immunohistochemistry, ELISA, and RT-PCR, Tsai *et al.* witnessed recovery from experimental uveitis by transgene expression following a single administration of rAAV-IL-1Ra at both the 10-day and 100-day timepoints.¹⁷

The demonstration of efficient rAAV-mediated transduction of corneal cells in both *in vivo* and *ex vivo* conditions has broadened the possible applications of rAAV-mediated gene therapy in corneal diseases to include inherited, iatrogenic, and metabolic diseases of the cornea.⁸ The work done by Liu *et*



al., 2008 encompassed an investigation of the tropism of a variety of rAAV serotype vectors in organ-cultured human corneas. The efficiency of transduction was marked by expression of the GFP reporter gene, which encodes the green fluorescent protein (GFP), and was delivered via the rAAV vectors. The observed transduction was extensive, reaching of a variety of corneal cells including those of the epithelium, endothelium, and keratocytes. Their findings hold great promise for treating a wide spectrum of corneal disorders; from a group of corneal dystrophies where the causative gene has been deduced to a single mutation in the transforming growth factor- β -induced gene, TGFBI/BIGH3, to others diseases where the genetic components remain either unknown or are multi-faceted. As demonstrated by the work of Liu *et al.* 2008, rAAV-mediated gene therapy can be used to target specific corneal cells, in which it could alter the expression levels of known mutant genes.

rAAV-Mediated Gene Therapy for Optic Neuropathies

The optic nerve is a unique ocular tissue because it originates in the eye yet functions in the nervous system by carrying the electrical impulses it receives from the retina to the brain. The axons of retinal ganglion cells converge into fiber bundles along the base of the inner retina, forming the optic nerve. Optic neuropathies encompass all conditions in which the optic nerve incurs any damage. Ocular rAAV-mediated gene therapy for the optic nerve involves both gene replacement and gene addition approaches, to which optic

neuropathies such as Leber's hereditary optic neuropathy and glaucoma are amenable.^{2,1}

Inherited Optic Neuropathies

Leber's hereditary optic neuropathy (LHON). Leber's hereditary optic neuropathy (LHON) is a common mitochondrial disease characterized by staggered, bilateral vision loss. As a maternally inherited disease, LHON primarily affects men during early adulthood. The disease is predominantly caused by three separate point mutations in genes that encode for the subunits of nicotinamide adenine dinucleotide: ubiquinone oxidoreductase, or complex I, an enzyme involved in the oxidative phosphorylation pathway.² Guy *et al.* recently implemented rAAV-mediated gene therapy to replace the G11778A mutation, which encodes for the ND4 subunit of complex I, and accounts for approximately 50% of all LHON cases. Guy *et al.* employed the use of an allotopic expression system for rAAV-mediated gene transfer of this G11778A mutation to the mitochondrial genome, since as a viral vector, the rAAV vector cannot directly transfer exogenous genes to the mitochondrial genome. The allotopic expression system expresses a nuclear-encoded version of a mitochondrial gene that encodes for a cytoplasmically expressed protein tagged with a mitochondrial-targeting peptide.^{18,2} Although Guy *et al.* were successful in restoring the cellular respiration deficit caused by LHON *in vitro*, an animal model for LHON does not exist, which limits investigation of the rAAV-mediated allotopic ND4 gene therapy approach *in vivo*.



Optic neuritis. Optic neuritis is a condition that causes inflammation of the optic nerve. People suffering from multiple sclerosis, an autoimmune disease of the central nervous system, are often susceptible to progressive visual loss due to recurrent episodes of optic neuritis. Specifically, in optic neuritis, autoimmune-mediated oxidative injury targets oligodendrocytes, cells that function as neuroglia in the central nervous system and produce the myelin sheath that surrounds retinal ganglion cell axons. The axonal demyelination that results in optic neuritis contributes to axonal degeneration and subsequent neuronal degeneration. Qi *et al.*, in their extensive work, have utilized the experimental autoimmune encephalomyelitis (EAE) rat model of multiple sclerosis in conjunction with rAAV-mediated gene therapy to probe the mechanisms that underlie the autoimmune-mediated oxidative injury observed in optic neuritis. Based on prior findings elucidating the damage-inducing role of reactive oxygen species (ROS), including superoxide and hydrogen peroxide in the EAE disease model,¹⁹ Qi *et al.* employed the use of the ROS scavengers superoxide dismutase (SOD) and catalase to develop an antioxidant gene therapy approach.²⁰

ROS are inducers of optic nerve demyelination and have also been found to interfere with the permeability of the blood-brain barrier in EAE. The ROS scavengers counteract the oxidative damage done by ROS, with SOD functioning in the dismutation of superoxide to hydrogen peroxide, and catalase detoxifying hydrogen peroxide to water and oxygen.^{21,20} The cDNA for extracellular superoxide dismutase (ECSOD) and catalase

was cloned into respective rAAV vectors, which were used to infect retinal ganglion cells of the rat EAE model by intravitreal injection. Relevant findings following transgene expression using both the rAAV-ECSOD and rAAV-catalase vectors included decreases in retinal ganglion cell loss by 29%, optic nerve demyelination by 36%, and axonal loss by 44%.²¹ Earlier results obtained by Qi *et al.* also demonstrated up to a 78% reduction in optic nerve demyelination in the EAE model.²⁰ The promising results elicited by the rAAV-mediated gene transfer of extracellular superoxide dismutase and catalase serve to demonstrate the great therapeutic potential as well as highlight the advantageous features of rAAV-mediated gene transfer for optic neuritis. rAAV-mediated gene transfer allows for a direct treatment approach, as antioxidant genes were delivered directly to the oligodendrocytes, whereas previous treatment approaches, such as catalase protein delivery, have been limited by incomplete penetration through the blood-brain barrier. Additionally, the long-term transgene expression enabled by the rAAV-mediated delivery of the ROS scavenger genes promoted long-term suppression of optic nerve demyelination and subsequent axonal degeneration.

Acquired Optic Neuropathies

Optic nerve trauma. Optic nerve trauma can result from any condition in which the retinal ganglion cells undergo axotomy, including transection of the optic nerve, which can ultimately lead to both neuronal and retinal ganglion cell death. Retinal ganglion cells experiencing optic nerve trauma are deprived



of brain-derived neurotrophic factor (BDNF), upon which they depend for survival. To better understand how optic nerve trauma can be treated, experimental optic nerve transection models have been developed.² rAAV-mediated gene transfer has been used as part of the treatment approach for optic nerve transection in a murine model. The ability of the rAAV vector to sustain long-term gene transduction proved advantageous for the work of Cheng *et al.*, who investigated the effect of upregulation of TrkB expression on retinal ganglion cell survival. Cheng *et al.* used rAAV-mediated gene therapy to transfer the gene encoding for TrkB, a BDNF receptor expressed by retinal ganglion cells, to the retinal ganglion cells in an optic nerve transection rat model. The researchers also supplemented TrkB transgene expression with direct administration of BDNF to the TrkB receptors. An increase in neuronal survival following optic nerve transection was observed.²²

Glaucoma. Glaucoma is a progressive optic neuropathy that likely results from the interaction of multiple genetic and environmental factors. While the predisposing genetic factors of glaucoma remain unknown, mutations in the gene encoding the myocilin protein have been found to cause autosomal dominant juvenile primary open-angle glaucoma, as well as nearly 3% of adult-onset open-angle glaucoma cases.²³ Many factors, including elevated intraocular pressure (IOP), can predispose an individual to developing the optic nerve head damage and eventual death of retinal ganglion cells characteristic of glaucoma. The implications

for rAAV-mediated gene therapy in the treatment of glaucoma are pervasive, given that gene therapy targets for glaucoma can range from structures to cell types, including the trabecular meshwork, ciliary body, retinal ganglion cells, and Müller cells.²³

Elevated intraocular pressure, which is widely known as the hallmark of glaucoma, is often accompanied by the accumulation of BDNF and its TrkB receptor at the optic nerve head. BDNF transport from the brain to the retinal ganglion cells of the inner retina is therefore interrupted, leading to BDNF deprivation of the retinal ganglion cells, and subsequent neuronal and retinal ganglion cell death. Previous work conducted by Ko *et al.*²⁴ demonstrated the limited survival of retinal ganglion cells in an experimental rat model of glaucoma following intravitreal injection of BDNF in conjunction with an intraperitoneal injection of a nonspecific free radical scavenger. Recognizing the limitations of multiple intravitreal injections of BDNF, however, Martin and Quigley used rAAV-mediated gene transfer to transfect retinal ganglion cells, also in a rat model of glaucoma. Using intravitreal delivery of rAAV-BDNF, a rAAV vector in which the cDNA for BDNF was enclosed, a 38% rescue of retinal ganglion cells from BDNF deprivation was witnessed.² The ability of rAAV-BDNF to slow the rate of retinal ganglion cell death, and thereby the overall progression of glaucoma, in a rat model highlights the relevance of rAAV-mediated gene therapy as a potential treatment for both polygenic diseases and those with unknown etiologies.



Another rAAV-mediated gene therapy approach implemented for the treatment of experimental glaucoma involves caspase inhibitors. Activated caspase enzymes are intrinsic to the initiation and regulation of apoptosis in retinal ganglion cells, specifically caspase-8 and caspase-3. McKinnon *et al.* investigated the role of modulating the activation of these caspase enzymes in increased retinal ganglion cell survival and subsequent optic nerve survival. The gene encoding baculoviral IAP repeat-containing protein-4 (BIRC4), a potent caspase inhibitor, was packaged into a rAAV vector and delivered to rat eyes by unilateral, intravitreal injection.²⁵ Ocular hypertension was then induced in the treated rat eyes to simulate the elevated intraocular pressure characteristic of glaucoma. Following a 12-week exposure to increased intraocular pressure, the rat optic nerve axons pretreated with rAAV-BIRC4 were counted and compared to balanced salt solution-treated control groups. On average 50% of the optic nerve axons in rat eyes expressing the BIRC4 transgene had been protected, compared with the control glaucoma eyes. The greater promotion of retinal ganglion cell survival by the rAAV-mediated transgene expression of the BIRC4 caspase inhibitor demonstrates the therapeutic potential that interrupting apoptosis of retinal ganglion cells has in the treatment of glaucoma. As a chronic optic neuropathy, however, glaucoma likely requires transgene expression for longer than even the yearlong expression that rAAV-mediated gene therapy can currently permit.^{25,2}

rAAV-Mediated Gene Therapy for Retinal Degenerative Disorders

The retina is the ocular structure predominantly involved in generating vision, converting light into electrical impulses and transmitting these signals to the brain. Therefore, the most severe forms of visual impairment are generally attributed to disorders in which the retina is implicated. The hallmark of all retinal degenerative disorders is the progressive apoptotic loss of the rod and/or cone photoreceptor cells of the retina. Nearly all retinal degeneration is either inherited or gene-based, making gene replacement therapy for such ocular diseases a potentially viable treatment option. Ocular gene therapy approaches in the retina include gene replacement, gene silencing, and gene addition, all of which target defective genes encoding the expression of proteins vital to photoreceptor function.^{1,3} The timing of vector and/or gene delivery is very significant in rAAV-mediated gene therapy for retinal degenerative disorders, since retinal degeneration can vary from early and severe to late and progressive. The retinal dystrophies that progress the fastest and have an earlier onset are the most difficult to treat, while slowly progressing degeneration has a wider therapeutic window.^{4,3} Certain retinal degenerative disorders have been found to be more amenable to treatment than others, such as Leber's congenital amaurosis, retinitis pigmentosa, and age-related macular degeneration.



Retinal degenerative disorders affect various regions of the retina, which spans nearly the entirety of the interior ocular circumference; therefore the retina can be divided into the peripheral retina and the central retina.

Inherited Degenerative Disorders of the Peripheral Retina

Leber's congenital amaurosis (LCA).

Leber's congenital amaurosis (LCA) is one of the most severe forms of an early-onset, inherited retinal degeneration and one of the most extensively studied disease models for retinal gene therapy. There are multiple forms of LCA that all share a common disease progression, featuring the onset of severe visual impairment from birth and a complete loss of vision by early adulthood (Smith *et al.*, 2009). Mutations identified in at least 12 different loci, including those in the *RDH12*, *RPGRI1*, *LRAT*, and *RPE65* genes, are currently thought to account for 50% of LCA cases. Mutations in *RPE65*, in particular, which cause a deficiency in production of the *RPE65* enzyme, have provided the most successful example of gene therapy intervention in the treatment of an ocular disease. The *RPE65* protein is localized in the retinal pigment epithelium and functions in visual cycle regulation by converting all trans-retinoids to 11-cis retinoids. *RPE65* deficiency interrupts this process and causes rod photoreceptors to become dysfunctional, leading to photoreceptor degeneration. Animal models of LCA have greatly facilitated experimental intervention with rAAV-mediated gene replacement, such as the *RPE65*-deficient murine model.

More significant, however, were the results of rAAV-mediated gene therapy in the larger, spontaneous *RPE65*-null model of LCA in the Swedish Briard dog, which demonstrated a persistent improvement in vision over an eight-year period following only a single administration of rAAV-vector. Rod photoreceptor function was restored following subretinal injection of either the rAAV2- or rAAV4-vectored canine *RPE65* gene.^{1,3}

The promising results of pre-clinical research helped to launch LCA as the first ocular disease treated in gene therapy clinical trials. Since 2007, the safety and efficacy of rAAV-mediated gene therapy for treatment of the *RPE65*-deficient form of LCA has continued to be investigated in three separate Phase I clinical trials. In each of the three clinical trials, a subretinal injection of rAAV2/2-vectored *RPE65* was administered to three *RPE65*-deficient LCA patients, who were between the ages of 17 and 26 years old and suffered from varying degrees of visual impairment due to LCA. Additionally, procedural differences between each of the three trials featured divergence in promoter types, either a RPE-specific *RPE65* or chicken β actin (CBA) promoter, in surgical protocols and also different volumes of rAAV vector used for injection. Changes in vision due to rAAV-mediated treatment in LCA patients compared to control patients were also evaluated by a variety of measures including pupillometry, microperimetry, and Early Treatment Diabetic Retinopathy Study acuity testing.^{26,27,28} Despite these differences, all three Phase I trials revealed improvements in retinal sensitivity.



Although preclinical experimentation suggested the greater amenability of younger subjects to rAAV-mediated gene therapy, the success of the three independent Phase I trials has provided even stronger evidence of the need to investigate the specific therapeutic window for rAAV-mediated gene replacement in LCA patients.^{29,1,3}

In a one-year follow up for the first LCA clinical trial to become a Phase 1/2 safety and efficacy trial, none of the patients involved experienced adverse effects, and one patient demonstrated an unexpected gain in visual function. To better understand this patient's improved vision, investigators quantified the patient's foveal fixation in response to a series of dim targets that were contrasted with a range of luminances. One eye was used as a control, while the other eye was treated by rAAV-mediated gene therapy. Results revealed that foveal fixation was similar in both eyes, however a shift in foveal fixation to the region of the retina occurred in the treated eye. The researchers surmise that additional clustering of cone photoreceptors at the superotemporal region of the retina formed a pseudo-fovea, which accounted for the increased cone function and improved vision. This latest finding has introduced yet another application of rAAV-mediated gene therapy in the treatment of congenital blindness.³⁰

Retinitis pigmentosa (RP). Retinitis pigmentosa (RP) is one of the most prevalent inherited retinal diseases, affecting nearly 1 in 3000, and has a variety of inheritance

patterns including dominant, recessive, and X-linked.³¹ Initially, affected individuals present with night-blindness due to degeneration of their rod photoreceptor cells, which can lead to tunnel vision. Complete vision loss in an affected individual can arise once cone photoreceptor cells degenerate. Many of the genes encoding the numerous proteins involved in the phototransduction pathway are susceptible to mutation and lead to the defects in phototransduction in RP. For example, the X-linked form of RP, which accounts for 15-20% of all RP cases, is caused by a defect in the retinitis pigmentosa GTPase regulator (*RPGR*) gene. The *RPGR* protein product is thought to regulate the protein distribution in the connecting cilium by directing or restricting protein transport to the photoreceptor outer segment. Interestingly, this pathway is also implicated in the form of LCA caused by a defect in the *RPGRIP* gene by mislocalizing the *RPGR* protein, which has been found to anchor to the connecting cilium.^{31,3}

The rapid degeneration of rod photoreceptors in the autosomal recessive form of RP is caused by null mutations in several genes encoding proteins involved in both phototransduction and photoreceptor outer segment regulation. In the murine model of autosomally recessive retinal degeneration, *PDE6B^{rd1}* is an allele of the gene that encodes for the β subunit of the rod cGMP phosphodiesterase (β PDE), an enzyme vital to the phototransduction cascade. Meanwhile, another frequently used model for autosomal recessive RP is in mice containing a spontaneous mutation in the gene encoding the



MER protein tyrosine kinase (*MERTK*), which is localized in the retinal pigment epithelium and is required for the phagocytosis of photoreceptor debris. Many other spontaneous retinal degenerative animal models exist for recessively inherited RP, which have all contributed to the understanding of autosomally inherited RP progression.^{31,3}

While there are many challenges to treating early onset, rapidly degenerating retinal dystrophies such as the X-linked and recessive forms of RP with gene replacement therapy, the mutational heterogeneity of autosomal dominantly inherited diseases provides the greatest challenge to implementing rAAV-mediated gene therapy, which has extensive potential as a treatment for monogenic diseases. Unlike the aforementioned primary gene defects for the X-linked and autosomal recessive forms of RP, no single causative gene has been identified for autosomal dominant RP. Rather, more than 200 mutations in the *RHO* gene, which encodes the photoreactive pigment absorbed by rod photoreceptor cells (rhodopsin, or *RHO*), have been found to account for the dominantly inherited form of RP. The complexity of treating dominantly inherited retinal disorders lies in the fact that several mutations in one gene can cause the same RP disease phenotype. Therefore, implementing a treatment that is independent of the mutation and that can still correct the resulting defect has been the focus of investigative efforts. Specifically, the recent successes in the implementation of gene replacement with gene suppression have renewed the possibilities for rAAV-mediated gene therapy in the treatment of RP.³² While

gene knockout strategies have long been used for gene suppression, the development of RNAi technology has introduced the possibility for gene knockdown using shRNA and siRNA.

The limited assessment of retinal function afforded by earlier studies focusing on both mutation-specific and mutation-independent suppression of autosomal dominant RP in mouse models using either ribozymes or RNAi has driven the research efforts of Chadderton *et al.* The researchers first established suppression of *RHO* in transgenic mice carrying a wild-type human *RHO* transgene following rAAV2/5 delivery of the *RHO*-targeting shRNA, shQ1, by subretinal injection. Chadderton *et al.* then studied the effects of rAAV-shQ1-mediated *RHO* suppression in conjunction with endogenous *RHO* gene replacement in transgenic mice carrying a Pro347Ser mutant human *RHO* transgene. rAAV-shQ1 and the control vector rAAV-shNT were injected into one of each pair of *RHO* mutant eyes, and retinal structure and function were assessed by histology and electroretinography (ERG), respectively, at 10 weeks. Significant improvements in both histology and ERG were noted, with the retinal structure of Pro347Ser eyes treated with rAAV-shQ1 showing substantially greater outer nuclear layer thickness than rAAV-shNT-treated eyes at both 5 weeks and 10 weeks post-injection. More importantly, average ERG values for rAAV-shQ1-injected Pro347Ser eyes were two-fold greater than for rAAV-shNT-treated eyes at 10 weeks post-injection. The promising results of Chadderton *et al.* using the two-component strategy of gene suppression in



conjunction with gene replacement outlines the great potential of this approach for many other animal models of dominantly inherited disorders such as autosomal dominant RP.³²

Mutations in genes that code for proteins in the connecting cilia of photoreceptor cells manifest as RP as well as systemically in syndromes such as Usher and Bardet-Biedl syndromes. These syndromes are also known as ciliopathies, since the resulting dysfunctional protein products of genetic mutations are localized in many, if not all, ciliated cells throughout the body. Consequently, in addition to RP, widespread syndromic defects result from ciliopathies. Individuals suffering from Bardet Biedl Syndrome can present with issues ranging from polydactyly and renal abnormalities to mental retardation and hypogenitalism.³¹ Usher syndrome is the most common of the RP syndromes; affected individuals present with symptoms that include deafblindness and vestibular dysfunction. The syndrome consists of three subtypes, USH1, USH2, and USH3, which are categorized by their clinical phenotypes and causative genes. Cilial cells are generally implicated in the USH1 form of Usher Syndrome; genes with USH1-associated mutations encode proteins important to the development and regulation of organs of the inner ear as well as to structural and functional integrity of the retina.

Defects in the *MYO7A* gene have been found to correlate with the USH1B form of Usher syndrome. Mutations in *MYO7A* are thought to account for the retinal degeneration associated with USH1B in humans, since *MYO7A* expression is localized in numerous

cell types including retinal pigment epithelial and photoreceptor cells. In the naturally occurring *Myo7a*-deficient shaker1 mouse model of USH1B, however, affected mice present solely with hearing loss. While retinal degeneration is absent despite the *Myo7a*-deficiency of shaker mice, defective trafficking of melanosomes in the retinal pigment epithelial cells is thought to be attributable to the *MYO7A* mutation. Usher syndrome resulting from a defective *MYO7A* gene seems most amenable to rAAV-mediated gene therapy when the novel rAAV2/5 vector is used, as it facilitates the efficient transfer of larger gene constructs.^{31,3}

Inherited Retinal Degenerative Disorders of the Central Retina

Within the central retina, which is responsible for central vision, resides the macula. Central to the macula is the fovea, the area of the retina with the greatest density of cone photoreceptor cells. The macula mainly functions in visual acuity and color vision, and therefore degeneration of the portion of retinal pigment epithelium that nourishes macular photoreceptors or the macular photoreceptors themselves significantly reduces central vision.

Retinoschisis. Retinoschisis is a retinal dystrophy in which the structure, and subsequently the function, of the retina are greatly compromised. The X-linked recessive form of retinoschisis, known as juvenile retinoschisis, leads to the degeneration of the central retina. Specifically, the retina separates into several layers, primarily at the fovea, and can potentially lead to a retinal detachment.



Juvenile retinoschisis is caused by mutations in the *RS1* gene, which encodes for retinoschisin, an extracellular protein integral to the retina for cellular adhesion and tissue stability.^{33,3} Many studies investigating rAAV-mediated gene therapy in a *RS1* knockout mouse model of human X-linked retinoschisis have demonstrated improvements in retinal function. Few studies, however, have shown restoration of the structural integrity of the retina. Min et al. found significant improvements in both retinal structure and function of 15-day old *Rs1h*-deficient mice following subretinal delivery of human *RS1* cDNA via the rAAV5 vector. The structure and function of the retina in the *Rs1h*-deficient mice was restored to levels comparable to those in wild-type mice and was long-term, persisting for up to a year.^{33,34}

Achromatopsia. Achromatopsia is a rare autosomal recessive congenital disorder that can render patients completely colorblind. Additionally, affected individuals often present with poor visual acuity, photophobia, and/or nystagmus.³¹ In general, achromatopsia is characterized by slow progression of cone photoreceptor dysfunction that can lead to one of two known forms, complete or incomplete achromatopsia. The two forms bear phenotypic resemblance, with the only difference being that incomplete achromatopsia patients have slightly better visual acuity and cone function. The two forms, however, are often genetically heterogeneous: three different genes have been found to be implicated for achromatopsia-associated mutations. Of these three cone-specific genes (*CNGB3*, *CNGA3*, and *GNAT2*), only *CNGA3* has been associated with both forms of achromatopsia.^{31,1}

Although both murine and canine models of achromatopsia exist, results of rAAV2/5-mediated gene therapy interventions in the naturally occurring dog model of achromatopsia are still at the preliminary stage. However, the rAAV2-mediated gene replacement of *GNAT2* in 2-3 week old *Gnat2*-deficient mice has resulted in marked improvements in achromatopsic pathology. Cone electrophysiology and visual acuity, which are both directly dependent on cone photoreceptor function, were restored to wild-type levels for as long as 7 months following subretinal administration of rAAV2-GNAT2 in the *Gnat2*-deficient mouse model.¹ Improving cone function is the goal of rAAV-mediated gene therapy for achromatopsia; it has been noted that success of gene therapy in as a potential therapeutic may depend on the age at which patient receives treatment.³

Stargardt disease. Stargardt disease is the most common form of juvenile macular dystrophy and has a recessive inheritance pattern. Degeneration due to Stargardt disease usually presents itself within the second decade of a patient's life and is characterized by progressive loss of central vision due to subretinal deposition of lipofuscin-like material in the macula.^{1,3} *ABCA4*, the large gene responsible for the development of Stargardt disease, encodes for the *ABCA4* transporter protein. *ABCA4* functions in the transport of a visual cycle retinoid byproduct, known as N-retinylidene phosphatidylethanolamine (N-RPE), across the outer segment membrane of photoreceptor discs to the retinal pigment epithelium. When any one of the nearly 400 mutations found to be associated with Stargardt disease are present in the *ABCA4*



gene, the dysfunctional transporter protein product triggers a cascade that first causes N-RPE to accumulate in the outer segment membrane of photoreceptor discs. The build up of N-RPE then leads to generation of the lipofuscin component N-retinylidene-N-retinylethanolamine (A2E), which causes lipofuscin deposits to form in the subretinal space between the retinal pigment epithelium and photoreceptors, and ultimately leads to photoreceptor degeneration.^{31,35}

Further investigation of Stargardt disease at the experimental level has been enabled through the development of an *Abca4*^{-/-} knockout mouse model. An increased accumulation of both A2E and lipofuscin was observed in the retinal pigment epithelium of *Abca4*^{-/-} mice, as was subsequent photoreceptor degeneration and abnormal electrical activity of photoreceptors.^{31,1} Until recently, gene therapy approaches for Stargardt disease were limited due to the large size of the ABCA4 cDNA and limited packaging capacity of rAAV vectors. However, rAAV-mediated gene therapy was successfully implemented in the *Abca4*^{-/-} mouse model using rAAV2/5-based vectors, which have been shown to efficiently package recombinant genomes up to 9kb in size. Following subretinal injection of the rAAV2/5 vector encoding the *Abca4* murine gene in the *Abca4*^{-/-} mouse model, a significant improvement was observed in retinal morphology and function owing to a corresponding reduction in lipofuscin accumulation.^{1,3}

Age-related macular degeneration (AMD). Age-related macular degeneration (AMD) is the leading cause of visual loss among the elderly population in many countries, including the United States. While there is no known single causative factor of AMD, both genetics and the environment are thought to play predominant roles in development of the disease. Central vision loss is characteristic of AMD since the macula deteriorates as the disease progresses. Consequently, experimental investigation of AMD has been complicated by the fact that most of the mammalian models available lack the macular region of the retina. However, numerous murine models of AMD have greatly elucidated the physiology and genetics behind AMD.³⁶

AMD is phenotypically heterogeneous, manifesting in one of two forms: the “dry,” non-exudative form or the “wet,” exudative form of AMD. “Dry” AMD is the more prevalent of the two forms and causes a milder phenotype, in which a yellowish-white substance called drusen is deposited just beneath the retina in the space between the retinal pigment epithelium and Bruch’s membrane. The deposition of drusen causes death of the retinal pigment epithelial cells and subsequent degeneration of the photoreceptors. Eventually, geographic atrophy occurs as the retina thins and vision worsens. Wet AMD is easily differentiated from dry AMD; wet AMD progresses rapidly and results in much more severe vision loss due to neovascularization of the choroid. The associated visual impairment progresses rapidly



once the blood leaks from the neovasculature into the subretinal region and thus damages the retina.³¹ Although both the phenotypic and environmental heterogeneity inherent between the two forms of AMD contribute to notions suggesting the two forms should be treated as two distinct diseases, recent genetic studies have linked polymorphisms in the complement factor H (CFH) gene to both the wet and dry forms of AMD.²²

Gene therapy approaches for treatment of dry AMD are limited; however, the recent finding of a genetic variant in the gene encoding the toll-like 3 (*TLR3*) receptor has expanded the possibilities for therapeutic intervention. Specifically, Yang *et al.* tested for an association between the functional *TLR3* variant, which involves the substitution of phenylalanine for leucine at amino acid 412, with AMD. Their results demonstrated an association between the *TLR3* variant and protection against the geographic atrophy indicative of dry AMD, which is thought to be mediated by suppression of retinal pigment epithelial cell death. However, no association with the choroidal neovascularization (CNV) phenotype of wet AMD was observed.³⁷ On the other hand, several rAAV-mediated gene therapy approaches have been implemented in the treatment of an experimental model of choroidal neovascularization. rAAV-mediated gene therapy has been used in both the induction and inhibition of choroidal neovascularization in the rat disease model. First, induction of choroidal neovascularization was adapted in the development of the rat model of wet AMD through subretinal delivery of

rAAV-vector encoding vascular endothelial growth factor (VEGF), a pro-angiogenic factor. Subsequently, the injected rats presented with the common symptoms of exudative AMD, including subretinal neovascularization, photoreceptor degeneration, and blood leakage of the neovasculature.³⁸

rAAV-mediated gene therapy has also been used to inhibit experimental models of choroidal neovascularization in a variety of animal models including mice, rats, and monkeys.^{39,40} Mori *et al.* have observed a reduction in both the development of CNV, as well as the regression of already developed CNV in a murine model following subretinal and intravitreal delivery of rAAV-vector encoding the pigment epithelial derived factor (PEDF), an anti-angiogenic, neurotrophic protein.³⁹ The many pre-clinical studies using rAAV-mediated gene therapy, especially in the investigation of wet AMD, hold great promise for clinical trials using rAAV-mediated gene therapy. Clinical trials employing the use of alternative gene therapy methods to treat wet AMD are currently underway.⁴¹ A few trials focus on gene suppression of VEGF and its receptor using siRNA targeting. Another trial employing adenoviral vector-mediated delivery of PEDF has successfully been completed. As mechanisms of AMD pathology continue to be unveiled, such as the role of inflammatory pathways in the progression of AMD and the susceptibility of retinal pigment epithelial cells to damage, the potential of intervention with rAAV-mediated gene therapy for use in clinical trials is significant.



Acquired Retinal Degenerative Disorders

Retinal neovascularization. Retinal neovascularization is a common feature of many ocular diseases, including the neovascular form of age-related macular degeneration, as previously mentioned, and is caused by many of the same aforementioned factors. rAAV-mediated gene therapy for treatment of retinal neovascularization in acquired diseases has far-reaching implications, since acquired diseases such as diabetic retinopathy and AMD account for the majority of cases of irreversible blindness in the world.⁴² In a long-term study investigating the therapeutic potential of rAAV-mediated expression of a soluble form of the Flt-1 (sFlt-1) receptor in inhibiting the angiogenic action of VEGF, Lai et al. observed a reduction in retinal neovascularization. Additionally, morphologic studies suggested preservation of retinal structure, unlike the retinal damage that commonly accompanies retinal neovascularization by inducing photoreceptor loss.⁴⁰

Gene Therapy Simultaneously Targeted to Retinal Rod and Cone Cells

While most of the rAAV-mediated gene therapy interventions for retinal diseases discussed here target either the rod or the cone photoreceptors, it is useful to treat the cell types simultaneously as both are implicated in retinal disease pathology. Furthermore, mutations in specific rod photoreceptor genes

can contribute to cone death as well as rod death, whereas ocular diseases caused by cone-specific mutations result only in cone death. To better understand the mechanism behind non-autonomous cone death, Punzo et al. studied the incidence of cone death in four different mouse models for retinitis pigmentosa. The researchers found a connection between cone survival and insulin release; non-autonomous cone death was triggered when cone photoreceptors were starved from a lack of endogenous insulin.⁴³

Other research efforts seeking to treat both rod and cone photoreceptor cell death have unveiled rAAV-mediated ocular gene therapy approaches that target expression of both cell types. The work of Khani *et al.* introduced the first well-defined, compact promoter to drive transgene expression in both rods and cones. Khani *et al.* compared the promoter activity of the human rhodopsin kinase (hRK), a gene which has previously been identified as both rod- and cone-specific, with the mouse opsin (mOps) promoter. While both promoter types yielded significant rAAV-mediated transgene expression following subretinal injection, only the hRK promoter demonstrated expression in both rods and cones, whereas the mOps promoter was active only in rod photoreceptors. This primary finding holds great significance for rAAV-mediated treatment of numerous retinal diseases, which has previously been limited by the lack of well-defined, rod/cone-specific promoters.⁴⁴ The same team of investigators demonstrated proof-of-principle of their



2007 findings in mouse models with defects in the *AIPL1* gene. Mutations of this gene show allelic heterogeneity, with a null allele resulting in a presentation similar to that of human LCA in mice, and the hypomorphic allele manifesting similarly to human RP in mice. Sun *et al.* assessed the role of rAAV-mediated gene expression of *AIPL1* using hRK to promote both rod and cone photoreceptor survival. Their results exhibited successful transgene expression in both rods and cones from the single hRK promoter.⁴⁵

Looking Ahead: Promising Prospects for Ocular Gene Therapies

Most recently, the therapeutic potential of rAAV-mediated gene therapy was yet again illustrated by Mancuso *et al.*, who studied the effects of rAAV-mediated intervention on colorblindness in adult primates. Colorblindness is one of the most prevalent X-linked recessive disorders in humans, and is a congenital condition in all male squirrel monkeys. Females of this species often have trichromatic color vision, meaning they possess all the necessary photopigments. The dichromatic male squirrel monkeys, however, lack either the L- or M-photopigment preventing them from distinguishing particular wavelengths. Mancuso *et al.* tested two adult male squirrel monkeys for color vision deficits using the Cambridge Colour Test. As expected, the two monkeys failed to discriminate between

red-violet and blue-green. These same two dichromatic squirrel monkeys lacking the L-opsin gene, were then given subretinal injections of an L-opsin coding rAAV 2/5 vector. The L-opsin transgene was co-expressed in a subset of endogenous M-cones in the primates, giving way to a shift in the spectral sensitivity of the M-cone photoreceptors. Mancuso *et al.* identified this very shift as the component underlying the transition from dichromatic color vision to trichromacy in the red-green colorblind adult primates, and that thereby corrected their colorblindness.⁴⁶ Many advances in experimental research have also fueled the success of rAAV-mediated gene therapy as a potential treatment for numerous ocular diseases. One such advance is the possibility of regulating the activation and deactivation of rAAV-mediated transgene expression by pharmacologically inducible expression systems.^{6,14} Intrinsic to any gene-regulated gene delivery system is an inducible promoter and a transactivator. An important consideration is the selection of the pharmacological agent used to induce any promoter system, several of which have already been identified as transgene expression regulators in eukaryotes. The development of pharmacologically regulated rAAV vectors has enormous implications for treatment of a wide variety of ocular diseases. The near future holds even greater promise for rAAV-mediated gene therapy in the treatment of ocular diseases.⁴⁷



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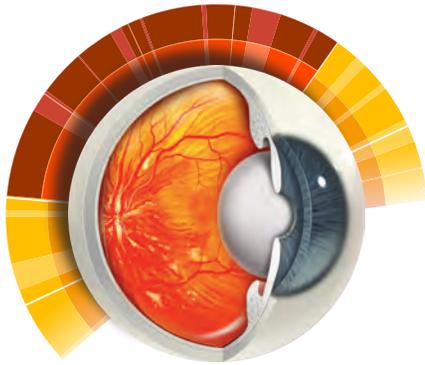
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