16 The Evolution of Ophthalmology in Rhode Island
GUEST EDITOR
MICHAEL E. MIGLIORI, MD, FACS

18 Glaucoma as a Neurodegenerative Disease: Why We Must ‘Look for the Protein’
LENWORTH N. JOHNSON, MD, MA (HON)

22 Selective Laser Trabeculoplasty as Primary Treatment for Open-Angle Glaucoma
LAITH M. KADASI, MD
SAFA WAGDI, MD
KIMBERLY V. MILLER, MD

26 The Role of Biological Agents and Immunomodulators in Treatment Strategies for Thyroid Eye Disease: An Evidence-based Review
ANNA GINTER, MD
MICHAEL E. MIGLIORI, MD, FACS

30 Corneal In Vivo Confocal Microscopy: Clinical Applications
JAE YOUNG YOU, MD
PAUL J. BOTELHO, MD
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June 2016 marks the 50th anniversary of the graduation of the first Rhode Island Hospital Ophthalmology Residency.

The Rhode Island Hospital Ophthalmology Residency Program was established in 1963, nine years before Brown University’s Program in Medicine was created. DR. ANTHONY BROCCOLI was recruited as its first ophthalmology resident. When the first medical school class enrolled at Brown in 1972, ophthalmology resident education was provided by a cohort of community-based physicians including DRS. H. FREDERICK STEPHENS (Ophthalmologist-in-Chief at RIH), ALEXANDER CALENDA, CHARLES DOES, JOSEPH DOWLING, JOHN MACIVER, RAYMOND MCKENDALL, LEO PRANIKOFF, NATHANIEL ROBINSON, and LIONEL SHEEHAN, all dedicated to teaching the next generation of ophthalmologists. The program, one resident per year, continued to graduate well-trained ophthalmologists and the number of voluntary faculty continued to grow under the leadership of DR. ROBERT KINDER, who became Ophthalmologist-in-Chief in 1978.

DR. WILLIAM TSIARAS became Ophthalmologist-in-Chief in 1989, and in 1993, the ophthalmology resident complement was increased to two residents per year. Voluntary faculty continued to provide resident education and supervision.

By 2004, RIH had five part-time ophthalmology faculty members who, along with several voluntary community-based faculty members, provided the didactic education and clinical supervision for the residents. Didactics and teaching conferences at RIH were supplemented by the addition of teaching conferences at the Providence VA Medical Center (PVAMC) in 2006. In 2007, to manage the continued growth of the patient care and the educational missions at the PVAMC, DR. PAUL GREENBERG, the Chief of Ophthalmology, became the first full-time Brown ophthalmology faculty member.

In 2013, RIH hired its first full-time faculty member, WENDY CHEN, MD, PhD, a pediatric ophthalmologist, followed shortly thereafter by LENWORTH JOHNSON, MD, a full-time neuro-ophthalmologist and Deputy Chief, and MICHAEL MIGLIORI, MD, full-time Chief of Ophthalmology. KIMBERLY MILLER, MD, joined as a full-time glaucoma specialist and Residency Program Director in August 2015. This increase in faculty complement was accompanied by an ACGME-approved increase in the training program to three residents per year.

The current ophthalmology faculty now numbers 45, with five full-time, 15 part-time, and 26 voluntary clinical faculty, as well as one basic science faculty member. This dedicated group of clinicians continues to turn out outstanding residents. Some of our faculty have been with the program for nearly 40 years, and a number of our graduates not only set up practice in Rhode Island, many of them continue to teach the next generation of ophthalmologists.

Over the last 50 years, ophthalmology as a specialty has evolved as well. The advances in technology with diagnostic imaging, lasers, and surgical instrumentation have made ophthalmic surgery extremely safe and effective. Almost all ophthalmic surgery is now performed as outpatient procedures, and most often under local anesthesia with sedation. Our understanding of ocular diseases has also evolved.

In this issue, DR. LENWORTH JOHNSON explores a novel concept in the evolution of understanding the pathophysiology of glaucoma. DR. LAITH KADASI, DR. SAFA WAGDI, and DR. KIMBERLY MILLER discuss a newer paradigm of laser therapy as initial therapy to treat open-angle glaucoma. DR. ANNA GINTER and I assess the current research on the mechanisms and targeted therapy of thyroid eye disease. DR. JAE YOUNG YOU and DR. PAUL BOTELHO describe corneal in vivo confocal microscopy, a new technology for the in vivo assessment of corneal pathology at the cellular level.

Ophthalmology is a fascinating specialty that combines medicine and surgery, old and new technology, and is constantly changing. It has been a joy to be a part of this training program for the last three decades, and the next 50 years looks even brighter.

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Rhode Island Hospital Ophthalmology Residency through 50 Years

View more photos
Glaucoma as a Neurodegenerative Disease: Why We Must ‘Look for the Protein’

LENWORTH N. JOHNSON, MD, MA (HON)

ABSTRACT
For years, clinicians and scientists interested in glaucoma have focused on the anterior segment of the eye and lowering of the intraocular pressure with respect to glaucoma causes and therapies. Yet glaucoma progresses in many individuals despite lowering the intraocular pressure. Herein, the concept of glaucoma as a neurodegenerative disease is presented.

KEYWORDS: actin, Alzheimer disease, cytoskeletal protein, cortactin, glaucoma, human genome, Huntington disease, intraocular pressure, neurodegenerative disease, optic neuropathy, DNA trinucleotide repeat.

INTRODUCTION
Glaucoma is a leading cause of blindness in the U.S. and worldwide [1]. Glaucoma is a group of diseases that features a progressive optic neuropathy accompanied by characteristic visual field changes, with or without increased intraocular pressure. Glaucoma has been aptly described as an “optic vasobaropathy” indicating that both vascular and mechanical pressure processes contribute to the optic nerve damage and visual loss [2]. Risk factors associated with the development of glaucoma include elevated intraocular pressure (> 21mmHg), increasing age, race [blacks more than whites], and a family history of glaucoma. Genes associated with glaucoma have been identified [3,4]. Other potential risk factors include diabetes mellitus, hypertension, myopia, cigarette smoking, and alcohol consumption.

GLAUCOMA AND INTRAOCULAR PRESSURE
A primary contributor of glaucoma development is a relative increase in intraocular pressure [IOP]. I use the term ‘relative’ because although a pressure greater than 21 mmHg is considered high, IOPs less than 21 mmHg could contribute to glaucoma [5,6]. High IOP results from a decrease in the outflow of aqueous fluid. The aqueous fluid is normally produced by the ciliary body in the eye and exits through the trabecular meshwork and Schlemm’s canal. The build-up of pressure in the eye is associated with retinal ganglion cell/optic nerve fiber loss which is exemplified by enlargement of the optic nerve cup-disc ratio and subsequent vision loss [Figure]. The Ocular Hypertension Treatment Study [OHTS] documented individuals without glaucoma, but who have high IOP, have a cumulative increased risk of developing glaucoma at 9.5% incidence in 5 years, or approximately 1–2% cumulative incidence per year [7,8]. Older individuals

Figure A. Optic nerve appearance of a patient with glaucoma with optic nerve cup-disc ratio of 0.6.

Figure B. Increased glaucomatous cupping from another patient with optic nerve cup-disc ratio of 0.8.
and those with thin (less than 555 microns) central corneal thickness measurements and large vertical cup-disc ratios [greater than 0.3] are more likely to develop glaucoma as the IOP increases.

The Collaborative Initial Glaucoma Treatment Study (CIGTS), Collaborative Normal-Tension Glaucoma Study (CNTGS), Early Manifest Glaucoma Trial (EMGT), Advanced Glaucoma Intervention Study (AGIS), and Glaucoma Laser Trial (GLT) have documented that reducing the baseline IOP by at least 20%, but preferably 30% or more, generally will prevent progression of visual field loss, even in patients with glaucoma who have an initial baseline IOP within the normal range (7–15). Accordingly, methods of lowering the IOP below the aforementioned 20% to 30% target pressure have been the mainstay of treatment for glaucoma, either by topical and/or oral medications, laser surgery [e.g., argon laser trabeculoplasty [ALT], selective laser trabeculoplasty [SLT]], conventional surgery or device placement [e.g., trabeculectomy, drainage implant device placement], or a combination of these therapies. However, despite lowering the IOP by these methods alone or in combination, there is still a cumulative 1–3% per year failure rate among individuals who received these treatments.

**IMPORTANCE OF LOOKING FOR THE PROTEIN**

Only 4.4% of participants without glaucoma in the OHTS who received treatment to lower the IOP developed glaucoma within 5 years in comparison with 9.5% of untreated participants. The OHTS clinical trial documented participants with high IOP without glaucoma at baseline had an approximate 50% reduction in glaucoma conversion at 5 years when IOP was lowered. But this meant the conversion to glaucoma continued in the other 50% of participants despite some of them having significantly lowered IOP, indicating that IOP is not the sole major factor causing glaucoma. We must look elsewhere. It is my impression that, “We must look for the protein.”

Most clinicians and scientists interested in glaucoma have focused on the anterior segment of the eye for glaucoma causes and therapies, in particular, evaluation of the trabecular meshwork and aqueous outflow mechanisms. The recognition that glaucoma is a neurodegenerative disease similar to Creutzfeldt-Jakob disease (CJD), Huntington’s disease, Alzheimer’s disease, Parkinson’s disease, myotonic dystrophy, amyotrophic lateral sclerosis (ALS, Lou Gehrig’s disease), chronic traumatic encephalopathy (CTE), and spinocerebellar ataxia, is now beginning to gain traction. There is a great need for further investigation of the retinal ganglion cells and their connecting neurons. It is my impression that glaucoma will be identified as a “protein-folding” neurodegenerative disease involving either a trinucleotide repeat [TNR] genetic disorder such as Poly-GAG (also called Poly-E) that could occur in actin or its fellow structural cell membrane protein component [e.g., actinin, vinculin, or cadherin], or a variable number tandem repeat [VNTR] genetic disorder as may occur in the cytoskeletal protein cortactin. Why might I suggest this?

**REDUNDANCIES IN THE HUMAN GENOME**

The haploid human genome consists of 23 chromosomes and 3 billion DNA nucleotide base pairs. The human genome contains approximately 20,000 to 25,000 protein-coding genes, with each gene comprised of approximately 4 exons, and each exon comprised of approximately 250 DNA nucleotide base pairs [16-18]. Given that there are 3 billion DNA base pairs of the haploid human genome, then the protein-coding genes comprise only about 1.5% of the total genome. The remainder of the human genome, the 98.5% which previously had been called “junk DNA,” is very important as it can be likened to a road map containing the following: regulatory sequences [enhancers, silencers, and locus control regions], promoter sites which bind RNA polymerases; introns, RNA genes [transfer RNA [tRNA], ribosomal RNA [rRNA], microRNA [miRNA], short nuclear RNA [snRNA], short nucleolar RNA [snoRNA], small interfering RNA [siRNA], and other non-coding RNA]; and repetitive non-coding DNA which accounts for 50% of the genome.

Genetic defects producing disease may arise from single nucleotide polymorphisms (SNPs) due to DNA nucleotide base pair substitutions, insertions, or deletions. These SNPs cause missense mutations by incorporating the wrong amino acid in the protein sequence [e.g., sickle cell anemia], nonsense mutations by incorporating an early stop signal [coded as TAG, TAA or TGA] causing a shortening of the produced protein, and frameshift mutation by causing a misreading of the 3-letter word DNA sequences due to the insertion or deletion of a nucleotide. Sometimes there could be large-scale rearrangements of the genome resulting in copy number variations (CNVs) which arise from insertion [translocation], deletion, duplication, or inversion of large segments of DNA at the time of meiosis resulting in haploid excess or haploid insufficiency. These CNVs cause genetic effects by increasing or decreasing the gene dose, or by influencing gene transcription and translation through position effects. The SNPs and CNVs alter the gene structure, function, or regulation, causing phenotypic changes or diseases [16-18].

**CHARACTERISTICS OF NEURODEGENERATIVE DISORDERS**

A relatively common CNV is the sequential repetition of several nucleotide base pairs. When 3 nucleotides are repeated, such as CAG being repeated several times, this is called a triplet nucleotide repeat or trinucleotide repeat [TNR]. When 6 or more nucleotide base pairs are repeated, this is called a variable number tandem repeat [VNTR]. Everyone has CNVs as a result of us normally having TNRs
or VNTRs. In general, it is when the number of these TNR or VNTR repeats exceeds a certain threshold that a disease is triggered [16-18]. Creutzfeldt-Jakob disease (CJD), the prototype of neurodegenerative diseases, is characterized by the presence of a transmissible particle, an abnormal prion PrP protein. Huntington’s disease [HD], another classic neurodegenerative disease, is inherited as an autosomal dominant trait and becomes manifest when, on chromosome 4, the normally occurring TNR ‘CAG’ (which codes for glutamine) is repeated more than 39 times. The normally occurring huntingtin protein now has an abnormal excess of glutamine [polyglutamine, poly-Q] resulting in the pathological hallmark of degeneration and atrophy of the neurons in the striatum and their connecting neurons in the cerebral cortex and other subcortical structures in HD [16-18].

FUNKY PROTEIN CELLULAR DEPOSITS

Like CJD and HD, neurodegenerative disorders have selective destruction of neurons within their associated neuronal network, and deposition of a “funky” or abnormal protein in the affected cell nucleus, cytoplasm, or both. This protein deposition can take the shape of plaques as with Alzheimer’s disease, neurofibrillary tangles as with chronic traumatic encephalopathy and Alzheimer’s disease, or inclusion bodies [Lewy bodies] in cytoplasm or nucleus as with Parkinson’s disease. The “funky” or abnormal protein that is translated from the TNR or VNTR gets cleaved by enzymes in the cytoplasm [16-18]. Some of the abnormal protein fragments will enter the nucleus and co-opt the nuclear machinery to make more of itself. The funky protein accumulates within the nucleus, cytoplasm, or both, thereby interfering with the cytoskeleton structure, cell signaling, or mitochondria energy generation machinery, thus killing the cell [18]. In the process, the transmissible protein is then passed on to other transsynaptic connecting cells causing selective neuronal destruction. In Parkinson’s disease, there is selective destruction of dopaminergic neurons in the substantia nigra and the neurons with which they synapse in the striatum of the basal ganglia and other brain regions. This results in the deposition of proteinaceous inclusion bodies [Lewy bodies] composed of alpha-synuclein protein. In fronto-temporal dementia [FTD] and chronic traumatic encephalopathy [CTE], there is selective destruction of neurons with deposition of tau protein. Alzheimer’s disease is characterized by accumulation of amyloid β protein forming senile plaques and tau protein forming neurofibrillary tangles in the nerve cell bodies, resulting in destruction of the cytoskeleton and eventual neuronal death.

There is an increasing body of work documenting glaucoma as a neurodegenerative disease with selective destruction of retinal ganglion cells, the connecting transsynaptic cells in the lateral geniculate nucleus, and occipital cortex [19]. Analysis of the vitreous in glaucoma, has shown an excess of glutamate [20]. The excess glutamate could be the result of a byproduct of cell death or could be part of the excess “funky” protein that is generated by having TNR or VNTR coding for excess glutamate which then causes cell death. I believe the latter. It is my belief that a potential TNR suspect is actin, a multifunctional protein involved in the cytoskeleton structure, and which normally has a TNR Poly-E [aka Poly-GAG] segment at the beginning of the gene, which could code for the translation of multiple glutamate molecules and abnormal protein folding [21-23]. Additionally, a potential VNTR suspect is cortactin, another cytoskeletal protein, which normally has a central 6.5 tandem repeat VNTR consisting of 30 amino acid sequence which also has the potential for coding for the translation of multiple glutamate molecules [21-23]. Indeed, recent studies have shown that mechanical pressure on a cell will cause abnormal actin cytoskeletal structural changes, potentially incapacitating the cell [21]. In conclusion, it is my impression that glaucoma will be identified as a “protein-folding” neurodegenerative disease. Like other neurodegenerative diseases, we should look for the protein in the retinal ganglion cells and their connecting neurons as this hopefully will expand our treatment armamentarium for this group of blinding diseases called glaucoma.

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ABSTRACT

Open-angle glaucoma is a silent, chronic disorder which results in progressive and permanent vision loss. Designing the optimal treatment regimen can be particularly challenging in the management of high-risk patients with frequent loss to follow-up or a longstanding history of medication noncompliance. In this article we aim to review fundamental techniques in glaucoma diagnosis and treatment with emphasis on the strengths and weaknesses of selective laser trabeculoplasty, a technique in modern therapy which may mold the future of primary treatment in open angle glaucoma management.

KEYWORDS: selective laser trabeculoplasty, glaucoma, laser surgery

INTRODUCTION

Glaucoma can be defined as a group of diseases that features a progressive optic neuropathy accompanied by characteristic visual field changes, with or without increased intraocular pressure. The most common form, primary open-angle glaucoma (POAG) is a disease that affects more than 2 million individuals in the United States, and is projected to increase to more than 3 million by 2020. It is characterized by a progressive, excavated optic neuropathy and is associated with stereotyped patterns of irreversible visual field loss which can eventually lead to blindness. Although the primary risk factors for this disease include the elevation of intraocular pressure (IOP), the presence or absence of ocular hypertension does not have a role in the definition of glaucoma itself. This article will review our current understanding of glaucoma diagnosis as well as an analysis of the benefits and weaknesses of selective laser trabeculoplasty, a technique in modern therapy which may mold the future of primary treatment in open-angle glaucoma management.

DIAGNOSIS

The identification of glaucoma can be challenging and requires careful assessment of multiple factors and diagnostic tests in order to establish POAG as a definitive diagnosis. Patients are often first established as glaucoma suspects on the basis of risk factors and receive an official designation of open-angle glaucoma following the assessment of IOP, gonioscopy, visual field deficits, and detailed assessment of the optic nerve and retinal nerve fiber layer itself.

Risk Factors

Accepted risk factors in primary open-angle glaucoma include race, specifically African and to a lesser extent Hispanic ancestry, advanced age, elevated intraocular pressure, cup-to-disc ratio, decreased central corneal thickness, and family history of glaucoma. Diabetes mellitus has a strong association with open-angle glaucoma, but remains controversial as a risk factor due to conflicting findings as an independent risk factor for disease among major studies.

Optic Nerve Assessment

In visualization of the optic nerve using ophthalmoscopy, it is beneficial to evaluate not only the cup-to-disc ratio, but also the distribution of tissue around the margin of the optic disc such as vertical cupping. Referral for ophthalmologic consultation in patients with an elevated cup-to-disc ratio or an atypical distribution of neuroretinal tissue at the optic disc will enable further assessment with Optical Coherence Tomography (OCT), an increasingly valuable screening tool which facilitates in the quantification of the retinal nerve fiber layer and ganglion cell layer of the retina, and can result in earlier detection of tissue loss in glaucoma suspects prior to the onset of visual field changes.

Goldmann Applanation Tonometry

The gold standard for obtaining the IOP measurement is via Goldmann Applanation Tonometry (GAT). This test requires the application of a prism mounted on the head of a tonometer against the corneal surface. The tonometer interface viewed by the clinician, adjusting the force applied to the tonometer head until the device indicates the force in mmHg necessary to flatten a 3.06mm diameter portion of the corneal surface. Ocular hypertension is considered pressure greater than 21mmHg. Alternative methods of intraocular pressure measurement are frequently used such as Pascal and ICare tonometry with concordance. These methods are more susceptible to error associated with abnormalities in corneal curvature and central corneal thickness, respectively.
Gonioscopy
Direct visualization of the anterior chamber angle is limited due to the phenomenon of total internal reflection. For this reason mirrors are applied in indirect gonioscopy to reflect light from the iridocorneal angle, allowing complete visualization of the trabecular meshwork in order to identify alternative causes of glaucomatous damage (Figures 1 and 2). This analysis includes identifying the presence or absence of neovascularization, or dense pigment deposition as seen in secondary open-angle glaucomas such as pigment dispersion or pseudoexfoliation. Furthermore, obscuration of angle structures can be seen in anatomically narrow angles, predisposing these patients towards angle closure glaucoma.

Visual Field
The gold standard for objective visual field assessment in glaucoma is known as automated static threshold perimetry. Visual field abnormalities do not appear until a substantial volume of ganglion cells are lost. Although several alternative methods of visual field measurement are available with variable sensitivity, Humphrey Visual Field testing remains the standard of care for glaucoma patients. Monitoring of characteristic visual field changes and progression remains a mainstay of glaucoma treatment.

MANAGEMENT
Although the pathogenesis of glaucoma remains poorly understood, successful treatment strategies at this time are directed toward lowering intraocular pressure due to a strong association with delay in the progression of glaucoma in treated patients. As a result, predominant trials in open-angle glaucoma therapy over the past several decades have been directed towards comparison among pressure lowering therapy in the form of topical medications, surgery, and laser trabeculoplasty. Designing the optimal treatment regimen can be particularly challenging in the management of high risk patients with frequent loss to follow-up or a long-standing history of medication noncompliance. Traditionally, open-angle glaucoma treatment is initiated with topical medications (Table 1), with the eventual consideration of treatment alternatives if there is failure to respond or medication noncompliance. The glaucoma laser trials supported consideration of a “laser first” approach due to the illustration that initial laser therapy was equally effective to topical therapy in direct comparison.

Figure 1. Photograph of the iridocorneal angle during gonioscopy. This image depicts an open angle with visualization of anatomical structures: A: Schwalbe’s Line, B: Nonpigmented Trabecular Meshwork, C: Pigmented Trabecular Meshwork, D: Scleral Spur, E: Iris.

Figure 2. Schematic of indirect gonioscopy. This image depicts the method in which gonioscopy can be used to view a reflection of the iridocorneal angle.
trials took place using an older method of therapy known as argon laser trabeculoplasty (ALT), which has been mostly replaced by a newer and safer alternative, selective laser trabeculoplasty (SLT).

Selective Laser Trabeculoplasty

Due to its extremely favorable safety and efficacy profile, SLT has gained acceptance as a mainstay in open-angle glaucoma management. In the coming decade, SLT is likely to become the primary therapy of choice in open-angle glaucoma, due to the safety and cost effectiveness of the procedure, the decreased burden of compliance on patients when compared with traditional therapies, and the ease with which retreatment and traditional operative interventions can be performed in post-procedural patients.

An important consideration in laser therapy safety and cost is the duration of procedure efficacy. Approximately 50% of eyes have been found to fail after SLT following a 2-year period, requiring retreatment. Selective Laser Trabeculoplasty remains a relatively young technique with limited data regarding the effects of repeated therapy over a 10-20 year course. These effects must be weighed against the adverse effects of long-term medication or multiple glaucoma surgeries, as patients using topical therapy for long periods of time frequently experience chemical irritation and delayed hypersensitivity reactions such as dermatoconjunctivitis medicamentosa. Similarly, traditional glaucoma surgeries have high complication and vision loss rates, making their use limited in early and moderate stage disease. Thus far the side effect profile of SLT compares favorably to those of medical therapy or surgical options, with an absence of systemic adverse effects and elimination of the procedural risks associated with operative monitored anesthesia care or general anesthesia in surgical patients. SLT has been associated with mild post-procedural redness, photophobia, and discomfort in the setting of transient anterior chamber inflammation with reported incidences ranging from 0% to 66%. A transient, 12-24 hour paradoxical increase in intraocular pressure has also been noted, which can be addressed prophylactically with IOP-lowering medications. Isolated observations of very rare complications such as peripheral anterior synechiae, hyphema, and corneal edema have also been described. Cost comparison studies directly assessing medical therapy and primary SLT over a 6-year horizon while assuming perfect drop administration efficiency rates have also found savings ranging from $200-3000 per patient, including adjustment for the potential need for retreatment every 2-3 years.

The decreased burden of compliance on patients is perhaps the strongest factor in considering SLT in this lifelong disease. A patient on bilateral maximal medical therapy using a combined ophthalmic preparation such as dorzolamide-timolol in addition to an alpha agonist and prostaglandin analog may be required to administer as many as 6 drops daily for life; if these drops are administered correctly the patient would wait 5 minutes following each when medication administration times coincide. In the presence of comorbid osteoarthritis, incoordination, or postural limitations the decreased efficiency of medication administration will further contribute to increased medical cost due to medication wasting and noncompliance.

CONCLUSION

Open-angle glaucoma is a devastating disease that presents many unique challenges in diagnosis and management. As the technique of SLT matures there will be an increasing body of evidence in support of the use of this technique as primary therapy.

Table 1. Topical Glaucoma Medications and Systemic Side Effects

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Common Topical Agents</th>
<th>Common Systemic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha 2 Adrenergic Agonists</td>
<td>Apraclonidine, Brimonidine</td>
<td>Dizziness, Fatigue, Headache, Insomnia, Myalgia, Nausea, Xerostomia</td>
</tr>
<tr>
<td>Beta Adrenergic Antagonists</td>
<td>Betaxolol, Cartelol, Levobunolol, Metipranol, Timolol</td>
<td>Bradycardia, Bronchospasm, CNS Depression, Heart Block, Hypotension</td>
</tr>
<tr>
<td>Carbonic Anhydrase Inhibitors</td>
<td>Brinzolamide, Dorzolamide</td>
<td>Acidosis, Blood Dyscrasias, Depression, Diarrhea, Hypokalemia, Nephrolithiasis</td>
</tr>
<tr>
<td>Parasympathomimetic Agents</td>
<td>Pilocarpine</td>
<td>Abdominal Cramps, Increased Salivation</td>
</tr>
<tr>
<td>Prostaglandin Analogues</td>
<td>Bimatoprost, Latanoprost, Travoprost</td>
<td>Arthralgia, Malaise, Headache</td>
</tr>
</tbody>
</table>

References


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Disclosures
None

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The Role of Biological Agents and Immunomodulators in Treatment Strategies for Thyroid Eye Disease: An Evidence-based Review

ANNA GINTER, MD; MICHAEL E. MIGLIORI, MD

ABSTRACT
Graves’ Disease is an autoimmune disease where circulating antibodies bind to the thyrotropin receptors on the thyroid gland. These bound antibodies mimic thyroid stimulating hormone without the normal feedback from the anterior pituitary, causing hyperthyroidism and thyrotoxicosis. These antibodies also interact with orbital tissues and cause the characteristic orbital findings of thyroid eye disease (TED). It is not clearly understood why anatomically and physiologically distinct tissues like the thyroid gland and orbit are affected selectively, or why the orbital disease tends to be self-limited. Identifying and understanding these processes is critical to targeting therapy.

In the active phase of the disease patients may experience orbital inflammation, eyelid and conjunctiva edema (chemosis), eyelid retraction, proptosis, ocular motility restriction, and optic nerve compression. Current treatment strategies for the ocular symptoms have been predominantly directed at symptomatic relief. More recently, investigators have concentrated their efforts to better understanding the underlying pathophysiologic processes to direct therapy at these processes. This review examines the current literature exploring a variety of newer therapeutic alternatives, including immunomodulative and suppressive agents, targeted at strategic points of the active-phase TED pathophysiological pathways. Specifically, biological agents including rituximab, adalimumab, intravenous immunoglobulin and others are reviewed with considerations for pathophysiology, extent of literature support, and adverse effects.

KEYWORDS: Grave’s Disease, thyroid eye disease, TED, TED treatment options

INTRODUCTION
Thyroid Eye Disease (TED) is the most common extra-thyroid manifestation of Grave’s Disease. [1] The annual incidence of TED has been estimated at 16 cases per 100,000 population for women, and 3 per 100,000 for men. [2] It is an immune-mediated disease and is most often associated with the immune thyroid diseases Grave’s disease and Hashimoto’s thyroiditis, but it can also occur with thyroid carcinoma, primary hyperthyroidism and neck irradiation. Up to 50% of patients with immune thyroid diseases develop TED, and of those, as many as 10% may develop severe inflammation, orbital congestion, impaired ocular motility, or compressive optic neuropathy. [3]

The range of TED treatment options varies depending upon severity, from topically palliative treatments including artificial tears, ointments, or prisms, to immunosuppressive agents such as steroids or cyclosporine, radiotherapy, and surgical decompression in more severe cases. Novel approaches to treatment have included anti-oxidant solutions containing selenium [4] and biological agents like rituximab and anti-tumor-necrosis-factor, among others. [5-7] This review considers the latter category of biological agents, examining briefly the agent, mechanism of action, existing evidence supporting their use, efficacy, and adverse effects. Some consideration will be also given to the role of biological agents in the context of overall TED treatment options, but a detailed consideration of all treatment options is beyond the scope of this biological agent-focused review.

RATIONALE FOR USE OF BIOLOGICAL AGENTS AND IMMUNOMODULATORS
Hyperthyroidism and TED, though temporally concomitant in many cases, may occur over 18 months apart, and even in the absence of one another. [8] Smoking [9] and poor control of the underlying thyroid disease have also being associated with more severe TED. [10] TED typically starts with an active inflammatory progression over 6 to 24 months (Fig.1), with expansion of extraocular muscles (EOMs) and surrounding fat (Fig. 2), often causing proptosis, impaired extraocular muscle movement, and in severe cases compressive optic neuropathy (Fig. 4). [11] Ultimately fibrosis and infiltration of glycosaminoglycans into the extraocular muscles result in the permanent changes seen in the chronic phase of the disease (Fig. 4).

Orbital fibroblasts are now considered the primary immunologic target in TED. Fibroblasts from patients with TED have been shown to express inflammatory cytokines, CD 34 and CD40. Pathophysiological studies in TED have also shown increased expression of thyrotropin receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-R1) on these fibroblasts.[12-14] Strategies, in turn, have been targeted at different components of the presumed pathophysiology.
Broad-spectrum anti-inflammatory and immunosuppressive agents

Corticosteroids, the mainstay of TED therapy, can be administered orally or systemically as intravenous (IV) infusions. However, current literature favors high dose systemic administration for severe active TED as reported by Kahaly, with greater positive clinical response in 77% of patient receiving IV methylprednisolone treatment vs. 51% of patients treated with oral prednisolone. (16) Similar response results were also reported for treatment of moderate active TED (17) by Aktaran et al with 72% responding to IV steroids vs. 49% responding to oral steroids.

Intraorbital injection of steroids are occasionally used to alleviate the acute orbital inflammation in TED. (18) In a prospective, single-blind randomized study (19) Marcocci et al evaluated cobalt radiation combined with steroid treatment, either administered systemically or locally by retrobulbar injection. Clinical improvement was noted in both groups, but there was significantly greater efficacy of systemic steroids compared to retrobulbar injection (60% vs. 30%) in severe active TED.

Antimetabolites form a group a potent immunomodulators. Azathioprine has not been shown to be of benefit as a single agent (20) but exhibits effectiveness when combined with radiation therapy or steroids. (21, 22) Methotrexate, although not commonly used, is effective as a sole treatment

Interestingly, only about one-third of moderate-severe TED sufferers are helped by traditional anti-inflammatory treatment options such as corticosteroids. (1,15) Hence, with the limitations of presently existing therapies and observed inconsistent associations between TED, thyroid disease, traditional anti-inflammatory treatment response, and smoking, the need for other therapeutic strategies is evident. Several such strategies, all at best incomplete and with varying efficacy, are discussed in the following sections on biological agents in TED, along with mechanisms of action and effects.

SPECIFIC AGENTS AND THEIR MECHANISMS OF ACTION

While few or no biological agents are exactly specific for a given target, a few have a thus far recognized preferential target (e.g. rituximab for B-lymphocytes). Hence, for purposes of our discussion below, we consider specific agents with specific targets. This discussion is cavedated with the following points: [1] a “pure target” and “pure agent” have not presently been discovered, so some additional effects may occur; [2] no single strategy has shown complete efficacy or “cure”; [3] some of these agents’ efficacy is extrapolated from analogous autoimmune diseases but actual human studies are either scarce or non-existent.

Figure 1. Active phase of TED with eyelid and orbital edema

Figure 2. CT scan showing asymmetric extraocular muscle enlargement in TED

Figure 3. Optic nerve compression from enlarged extraocular muscles

Figure 4. Chronic phase of TED with proptosis and lid retraction

Figure 5. Active phase of TED with proptosis and lid retraction

Figure 6. CT scan showing asymmetric extraocular muscle enlargement in TED

Figure 7. Optic nerve compression from enlarged extraocular muscles

Figure 8. Chronic phase of TED with proptosis and lid retraction
in patients who failed steroids. Another member of the antimitabolite family, mycophenolate mofetil, was noted to be not only effective but exhibited more effectiveness as a sole treatment than cyclosporine; however, the literature regarding this agent remains sparse. Moreover, no comparison of this agent to standard steroid treatment is found in the presently available literature.

The anti-oxidant agent selenium was evaluated against the anti-inflammatory agent pentoxifylline in 159 patients with mild Graves’ orbitopathy. The authors noted decreased clinical activity scores of TED in both treatment groups, with significant improvement in quality of life, reduced ocular involvement, and slowed disease progression in the selenium treatment group at the 12-month follow-up. This data suggests selenium oral supplements at a dose of 100ug, twice per day, appears a harmless adjunct to conservative management in early mild stages of TED.

**Anti-B-cell agents**

Rituximab (RTX), a monoclonal chimeric antibody against the transmembrane protein CD20 on B cells (but not plasma cells), has resulted in improved clinical activity score and efficacy over 18 months in several studies. A recent randomized, prospective study evaluating intraorbital injection of rituximab versus high dose of systemic glucocorticoids in the treatment of thyroid-associated orbitopathy demonstrated a therapeutic efficacy of RTX in active disease, even in low doses and locally administered, with the efficacy on the inflammatory component of the disease comparable to that of steroids and seemingly related with the reduction of peripheral CD20+ lymphocytes. Further studies are needed to fully evaluate efficacy and safety of rituximab.

**Anti-T-cell agents**

T-cells expressing IGF-1 receptors are thought to play an important role in mediating the autoimmune process in TED. Teprotumumab is a human monoclonal antibody that blocks the IGF-1 receptor, initially designed for treatment of solid and hematologic tumors; it is presently also undergoing phase 2 clinical trials in patients with active TED. A recent retrospective, limited sample-study showed that RTX also had an effect on reduction of IGF-1R+ T-cells, coinciding with clinical improvement at 4 to 6 weeks post-treatment.

Meanwhile, a study involving a 12-week treatment period with 11 patients treated with prednisone and 4 using cyclosporine found that combination therapy was better tolerated than prednisone treatment alone, while single-drug therapy with prednisone was found more effective than cyclosporine in patients with severe Graves’ ophthalmopathy. A separate study of 40 patients noted some role for cyclosporin with improvement of all signs of endocrine ophthalmopathy while administering cyclosporin-prednisone combination therapy.

**Anti-auto-antigen and intravenous immunoglobulin**

The hypothesis of an anti-auto-antigen targeting strategy may be supported by a recently published study which showed that thyroid stimulating but not blocking autoantibodies are highly prevalent in severe and active thyroid-associated orbitopathy. Therapeutic measures targeting the autoantibodies may be effective, though such consideration must be cautioned in determining whether the presence of such autoantibodies is truly causal or an epiphenomenon.

A randomized, controlled trial of 19 patients treated with 20 weeks of oral prednisolone vs. 21 receiving 1 g IVIG/kg body weight for two consecutive days every 3 weeks noted a comparable successful outcome between the two groups, with responders noted to have improved proptosis, visual acuity, intraocular pressure, lid aperture, and eye muscle area. In addition, thyroid antibody titers were reduced markedly in the IVIG group. However, the incidence of side effects was noted to be more severe in the steroid group, for which the authors suggested IVIG may be preferable to steroids for TED.

**Plasma Filtration**

A separate randomized study of 20 patients comparing IV methylprednisolone alone or in conjunction with plasma filtration found that while both groups improved their clinical activity scores, the change occurred more rapidly in patients treated with plasma filtration.

**Biologic response modifiers**

Various anti-cytokine-specific strategies have been evaluated in patients with different severity of TED. For example, in a small (10 consecutive patients) study, the TNF receptor blocker etanercept was found to improve the clinical activity score significantly for those suffering from mild-to-moderate TED. One case showed infliximab (monoclonal antibody against TNF) being successfully used in a sight-threatening TED resistant to oral steroids. Anti-TNF medication adalimumab (a fully human monoclonal antibody against TNF) may have a limited role in TED with prominent inflammatory symptoms, as noted in a small sample observer-blinded.

Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, mainly used in treatment of severe rheumatoid arthritis and juvenile idiopathic arthritis, proved to be effective when used in steroid-resistant active, severe TED in a small study of 18 patients, with improvement in proptosis in 72% of patients, extraocular motility in 83% of patients, and diplopia in 54% patients. However, this is a novel drug, and hence minimal data is available.

**Anti-Cell-Adhesion**

A prospective, randomized, controlled trial of colchicine (1.5 mg/day) vs. prednisone (0.75 mg/kg/day) in 22 patients during the inflammatory phase of Graves’ ophthalmopathy found improved clinical activity scores in 68% of the colchicine group. However, this is a novel drug, and hence minimal data is available.
treated patients, with signal intensity on MRI also noted to be improved; side effects were prevalent in the steroid group but absent in the colchicine group. [37] It has been proposed that colchicine is specific to neutrophil and endothelial cell adhesion, modulating chemokine and prostanoid production. [38]

Future Considerations
Not all novel treatments have shown promise. Somatostatin analogs, which may play a role in the development and regulation of T cells, have been shown to offer no improvement in TED patients in randomized controlled trials. [39-42] An interesting side effect of prostaglandin F2-alpha eye drops (bimatoprost), an agent used to treat glaucoma, is the development of orbital fat atrophy, termed Prostaglandin Associated Periorbitopathy. [43] This eye drop is undergoing a randomized, controlled, double-blind crossover trial in thyroid eye disease to assess its effect on the orbital fat of TED patients.

Animal models for auto-immune thyroid eye disease are limited, but some success has been achieved and described. [44] Though beyond the scope for detailed consideration in this review, such models, if they can accurately be extrapolated to human disease, could be very valuable in creating effective treatment modalities.

CONCLUSIONS
The data considered above suggests a role for different, newer agents, exemplified by wide-ranging predecessors such as selenium’s anti-oxidant properties (for milder TED) to anti-inflammatory and generally immunosuppressive properties of steroids or cyclosporin. Specific biological agents such as RTX have shown improvement, with IVIG and even anti-TNF medications having potential roles in specified symptoms. Patient selection for specific therapy, as well as a broader understanding of pathophysiology will likely lead to creation of more targeted therapies. These, in turn, must be evaluated in properly designed prospective, double-blinded, randomized, controlled trials.

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Corneal In Vivo Confocal Microscopy: Clinical Applications

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ABSTRACT

In vivo confocal microscopy (IVCM) has become a widely accepted imaging technique to study the human living cornea. It provides a unique opportunity to visualize the corneal tissue at the cellular level without damage and longitudinally observe its pathologic and normative changes. With rapidly evolving technology, there has been an abundance of interest in maximizing its potential to better understand the human cornea in health and disease. This is evidenced by a growing literature analyzing acquired and inherited corneal and also systemic diseases using corneal IVCM. This article provides a narrative review of IVCM and its applications.

KEYWORDS: In vivo confocal microscopy, cornea, infective keratitis, corneal dystrophy

INTRODUCTION

In vivo confocal microscopy (IVCM) is a non-invasive imaging tool that enables an in vivo examination of the cornea at greatly enhanced magnification. Recent advances have broadened its application in both research and clinical realms as they allow fast acquisition of high resolution images of living cornea and its microstructures. This article provides an overview of current research and clinical applications of this technology.

Optical principle of confocal microscopy

The main advantage of confocal microscopy is its ability to obtain images from selected depth by optical sectioning. It is achieved by focusing a light source through a slit, or an aperture, on a small area of the tissue and analyzing the reflected light only from the selected focal plane. The light from the out of focus planes is attenuated. As the scan progresses serially through various depths of the cornea, multiple optical sections are acquired, creating an en face image of corneal layers and its microstructures such as Langerhan cells, sub-basal nerves, keratocytes and endothelial cells.

Figure 1

The concept of confocal microscopy was first patented by Marvin Minsky in 1957 to study the brain neural cells. It was subsequently applied in various facets in ophthalmology, namely retinal and optic disc confocal scanning laser ophthalmoscopy. After numerous IVCM studies in ex vivo human eyes and in vivo rabbit eyes, the first in vivo images of the human cornea were obtained by Cavanaugh et al. in 1989. They demonstrated the confocal visualization of epithelium, basal lamina, Bowman’s layer, stromal nerves, pre-Descemet’s membrane and endothelium in living cornea. More importantly, it portended a new paradigm to bridge histopathologic knowledge to the living tissue and study the dynamic nature of the living eye.

Thus far, three main commercial confocal systems have been developed for in vivo corneal imaging, the Tandem Scanning Confocal Microscope (TSCM), the Slit Scanning Confocal Microscope (SSCM) and the Laser Scanning Microscope (LSCM). The first real-time TSCM was introduced in 1989. It was based on the modified Nipkow spinning disc technology which used a metal disc with multiple pinholes of 30 microns in size. The metal disc was rotated at high speed, allowing rapid acquisition. The small pinhole also provided a thin field of depth; however, it limited the light output that reached the detector to less than 1%. Then, SSCM was introduced in 1994 with improved light output throughout and faster acquisition time, however, at the cost of axial resolution. The axial resolution of SSCM ranged from 8 µm to 25 µm, in comparison to 9 µm to 12 µm in TSCM. LSCM was first introduced in 2003, comprised of Heidelberg retina tomograph (HRT) and Rostock Corneal Module. It rapidly scans a 670nm-diode laser beam and creates a high resolution image of 384 x 384 points in a 400 µm. This device provides a greater contrast than TSCM or SSCM with the superior axial resolution of 4 µm, but it is not as user-friendly as SSCM. Unfortunately, the quantitative measurements between different types of machines are not comparable due to differences in contrast and sectioning thickness. TSCM is no longer commercially available.

Clinical application of IVCM

The role of corneal IVCM in the clinical setting has expanded over the last three decades. IVCM characteristics of acquired and inherited corneal pathologies such as infectious keratitis of many organisms and Fuchs’ endothelial dystrophy have been extensively studied. Further, the quantification of IVCM parameters, including cell densities [epithelium, keratocytes and endothelium], sub-basal nerve plexus density, number, length, tortuosity and reflectivity and anterior stromal backscatter were tirelessly pursued. Through these
Figure 1. Representative IVCM images of normal cornea using SSCM (Confoscan 4, NIDEK, Gamagori, Japan) and LSCM (Heidelberg Retina Tomography II Rostock Corneal Module, Heidelberg Engineering, Heidelberg, Germany).

A and B demonstrate the corneal epithelium using SSCM and LSCM, respectively.

C and D show the sub-basal nerve plexus between basal epithelium and Bowman’s layer.

E and F show the corneal stroma.

G and H show the corneal endothelium.

SSCM images are sized 460 x 345 mm, LSCM images are cropped to 345 x 345 mm.


Infectious keratitis

The role of IVCM in the clinical setting has been the most highlighted in the management of infectious keratitis. While microbiology diagnosis via corneal scrape or biopsy remains the gold standard, IVCM renders early diagnosis and initiation of targeted antimicrobial therapy.

This is particularly useful in challenging cases such as contact lens-related keratitis. Acanthamoeba cysts measure 15–28 µm; the trophozoites measure 25–40 µm; fungal hyphae measures approximately 6 µm. They can be visualized using IVCM directly. In a prospective, double-masked, observational study that included 103 microbiologically-proven Acanthamoeba and fungal keratitis cases, the sensitivity of IVCM in the identification of Acanthamoeba cysts and fungal elements was 88.3% and specificity was 91.1%. This early diagnosis may have a profound impact on visual outcome. The American Academy of Ophthalmology reported level II
evidence for the adjunctive role of IVCM in the diagnosis of Acanthamoeba keratitis.11

The sub-basal nerve and dendritic cell densities in herpetic simplex keratitis and herpes zoster ophthalmicus have also been studied extensively. The loss of sub-basal nerve density has been shown to be a prominent feature in IVCM along with increased dendritic cell density in the basal epithelium and squamous metaplasia.12,13 The loss of sub-basal nerve correlates with the clinical loss of corneal sensation.13 These characteristics can help diagnose herpetic keratitis in complex cases.

The sub-epithelial infiltrates in patients with epidemic keratoconjunctivitis has been associated with increased dendritic cell density in the basal epithelium and Bowman’s layer.4 On the other end, the use of IVCM in bacterial keratitis has been limited, as the organisms are generally beyond the resolution of IVCM.4

Post-surgical changes
IVCM has contributed greatly in understanding the healing process of the cornea after refractive surgeries. Using IVCM, we learned that it may take up to one month for epithelial architecture to return to normal following photorefractive keratectomy [PRK].14 Also, the sub-basal nerve density is not fully recovered until two years after PRK and five years after laser-assisted in situ keratomileusis [LASIK].14 Additionally, IVCM has been instrumental in demonstrating the efficacy of using mitomycin-C with PRK.15 Post-PRK haze is correlated to increased cellular reflectivity due to activated keratocytes. Gambato et al. performed a randomized controlled study of corneal wound healing following PRK and observed a reduction in the IVCM appearance of activated keratocytes and clinical corneal haze with application of mitomycin C in high myopic patients.12

Most of our current knowledge in cellular changes after corneal transplant come from animal models or ex vivo issues. Real-time observation of wound healing process after various keratoplasty techniques has become possible with IVCM. A longitudinal study found that only 53% of subjects re-innervated with anterior stromal nerves in the central cornea at 12 months following penetrating keratoplasty and the regenerated nerves have abnormal morphology such as increased tortuosity.16

IVCM has also been implicated as a potential tool to monitor subclinical cellular changes after corneal transplant.17 A prospective observation study monitored the keratocyte counts in the anterior, middle and posterior stroma for two years following penetrating keratoplasty and demonstrated that the increase in the AK counts was seen two months before the clinical diagnosis of rejection. This was followed by the normalization of keratocyte count after intensive anti-rejection regimen, comparable to the group that did not have clinical signs of the graft rejection.17 The ability of IVCM to detect signs of rejection prior to clinical signs will allow early diagnoses, treatment of corneal rejection and successful corneal transplants.

Corneal dystrophy
The use of IVCM has enabled us to visualize the pathophysiology of many corneal dystrophies in vivo. While ex vivo specimen allowed the studies of end-stage disease, we are now able to follow the changes occurring over the course of the disease. We are also able to screen the affected family members for some inheritable corneal dystrophies.4 IVCM is also being used to newly classify the severity of corneal dystrophy. A good example is seen in Fuchs’ endothelial dystrophy.18 The traditional grading, based on the extent of guttata and corneal edema, is inadequate in the era of DSAEK and DMEK. IVCM has demonstrated early factors associated with increased anterior corneal backscatter, abnormal sub-basal and stromal nerve density and decreased anterior keratocyte densities.18 These parameters are being studied with the goal of achieving an objective method of assessing disease severity.

Additionally, in complex cases of corneal dystrophy, IVCM is increasingly utilized to diagnose one or more diseases.19

Peripheral neuropathy
The cornea is the most densely innervated part of the human body. It has emerged as a promising region to study systemic peripheral neuropathies.2 Using IVCM, we can quantify sub-basal nerve damage as a surrogate for the severity of peripheral neuropathy.2 This allows early detection, diagnosis and treatment response. Its possible role in detecting and managing nerve damage has been studied in diabetes, Parkinson’s disease, amyotrophic lateral sclerosis and chemotherapy-induced peripheral neuropathy.20 Studies have shown that decreased subbasal nerve density is associated with symptoms of peripheral neuropathy. Further, the loss in corneal subbasal nerves precede any clinical signs or symptoms of neuropathy, retinopathy and nephropathy.20 Interestingly, IVCM has been shown to detect early nerve regeneration after pancreas transplantation in patients with type I diabetes. This is an especially exciting application of IVCM, as it can potentially benefit a large number of patients.

FUTURE DIRECTION
IVCM has broadened our understanding of the cornea in a profound way, offering a unique window to examine in vivo cornea tissue in health and disease and quantify corneal pathology. It has yet to reach its peak. Advancing technology in software and engineering, standardized acquisition, establishment of baseline values and development of software for automated analysis are some of the areas that will increase its accessibility and application in both research and clinical arenas. Regardless, with rapidly evolving technology, it continues to be a powerful clinical tool in vision science.
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Disclosures

None

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The Role of Biological Agents and Immunomodulators in Treatment Strategies for Thyroid Eye Disease: An Evidence-based Review

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