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I am deeply honored to have been asked to present the tenth annual Hoyt Lecture. No one has had more influence on modern neuro-ophthalmology than William Hoyt. The list of students, residents, and fellows whom he directly mentored, or who were indirectly touched by his trainees, is too long to enumerate. In particular, Bill's contributions, including the clinical vignettes in the third addition of Clinical Neuro-ophthalmology, his meticulous approach to patients, and his ability to adapt to new technology, have served as a model and inspiration for all of us.

In ophthalmology, as in other areas of medicine, some people fix things, and others of us teach those individuals what to fix. Neuro-ophthalmology has traditionally had as its primary goal, the diagnosis of visual system pathology. As such, this "cognitive" branch of ophthalmology has largely been separated from therapeutics. David Cogan, M.D. stated that “Neuro-ophthalmology shares with neurology in general, limited therapeutic successes. Its strength is largely diagnostic, rather than therapeutic.”[1] Yet, this has changed dramatically with advances in neuroimaging and neuro-therapeutics. As neuro-ophthalmologists, we are going to be asked increasingly, if not to play a primary interventional role, then to be involved in making decisions about when and how intervention takes place.

In the last three to four decades, there has been a paradigm shift to quantification of the three diagnostic pillars of our specialty: anatomy, physiology, and psychophysics.[2] The study of clinical neuro-anatomy has been revolutionized with the introduction of neuroimaging techniques such as computed tomography (CT) [3,4] and magnetic resonance imaging (MRI). [5,6] Optical coherence tomography (OCT) is a revolutionary technology for examining various parts of the eye including the nerve fiber layer and optic disc. Future advances will likely permit us to segment the various components of the proximal visual pathways. [7] Physiology can now be quantitated through a variety of electrophysiologic tests, including electroretinography (ERG) and visual evoked potentials (VEP).[8] In recent years, these technologies have been improved to the point that we can now examine specific areas of the retina or the visual field with the advent of multifocal ERG and VEP. Finally, the development of automated perimetry has allowed standardization and thus increasing reproducibility of visual field testing. [9] In addition, new psychophysical techniques have been devised to study the visual field in more rapid and specific fashion, including frequency doubling technique and short wavelength automated perimetry. Simple measures of physiologic function such as the afferent pupillary defect may also be quantified. [10] Although more than 100 years old quantification of relative movements of the two eyes as described by Walter Rudolph
Hess (one of three ophthalmologists to win the Nobel prize) has been largely underutilized.\cite{11}

It is this application of quantitation that will permit us as neuro-ophthalmologists to better understand the natural history of disease and the options for therapeutic intervention. In the future we as neuroophthalmologists will increasingly be called upon to apply these quantitative techniques to recommend, guide and actually direct therapy. It is the combination of the neuro-ophthalmologist becoming more involved in therapeutics, and the creation of more accurate and reproducible techniques to qualify our clinical findings, that form the basis of my lecture. I will approach this in four major categories: 1) how the neuro-ophthalmologist may assist in diagnosis, 2) what the neuro-ophthalmologist can treat; 3) how the neuro-ophthalmologist can assist with treatment; 4) how the neuro-ophthalmologist can provide advice for a variety of treatment decisions. In the tradition of the 3rd edition of Clinical Neuro-Ophthalmology, I would like to illustrate my lecture with a series of clinical case presentations.

**How the neuro-ophthalmologist may assist in diagnosis**

While the advent of high-resolution neuroimaging techniques has improved anatomic localization of a disease process these studies are not specific and often obtaining tissue for pathologic examination is required. A 57-year-old man presented with a three-week history of periorcular pain and horizontal diplopia. He was found to have limited abduction of the right eye. While he was presumed to have a VIth nerve palsy quantitative elevation of intraocular pressure with abduction suggested medial rectus restriction and an orbital CT confirmed a mass involving the right medial rectus muscle [Supplementary Figure 1]. Fine needle aspiration biopsy (FNAB) of the mass was small blue cells which stained for serotonin [Supplementary Figure 2] diagnostic of metastatic carcinoid tumor. The patient was treated with endocrine suppression and radiation therapy.

Modifications of Jack Kennerdell’s orbital FNAB \cite{12,13,14} permit us to reach skull base lesions. A 68-year-old woman was referred with a six-week history of diplopia and was found to have a right sixth nerve palsy [Supplementary Figure 3]. Review of her CT scan (previously read as normal) demonstrated a suspicious area in the region of the right cavernous sinus, which was better defined on MRI [Supplementary Figure 4]. To reach this area of the skull base, I adapted the technique used by neurosurgery for percutaneous trigeminal rhizotomy,\cite{15,16,17} Using the Stealth neuronavigation system [Supplementary Figure 5] to access the posterior cavernous sinus through the foramen ovale, cellular elements were obtained, revealing B cells, which stained for CD10 and CD\cite{19}. The patient was spared a craniotomy, and her lymphoma was treated with radiation therapy. This technique has been particularly useful in separating benign from malignant pathology.\cite{18,19,20,21}

Improvements in our understanding of the growth and spread of neoplasia may direct us to less invasive means of obtaining tissue for a diagnosis. One good example of this is our recognition of the tendency of certain tumors (especially squamous cell carcinoma and adenoid cystic carcinoma) to spread along nerves.\cite{22,23,24} These may be difficult to diagnose especially if imaging is unremarkable.\cite{25,26,27} This 63 year old patient was referred for double vision and facial numbness. He had evidence of difficulty with down gaze and absent sensation over V1 and V2 [Supplementary Figure 6]. Nineteen months earlier a lesion his dentist noted on his cheek. A punch biopsy revealed squamous cell cancer, but his Mohs surgery “was negative.” Six months later he developed numbness on his cheek and over the subsequent thirteen months had four
MRI scans, all of which had been read as negative. Review of his last MRI scan revealed enhancement in his inferior cavernous sinus [Supplementary Figure 7]. He was referred to neurosurgery for a craniotomy but instead the diagnosis was confirmed by transantral biopsy of his infraorbital nerve which was, as expected, filled with squamous cell carcinoma [Supplementary Figure 8]. The patient underwent radiotherapy.

What the Neuro-ophthalmologist Can Treat

Eye muscle surgery often plays a critical role in rehabilitation of many of our patients who present with strabismus of restrictive or paretic cause. The goal of any strabismus surgery is not only to give the patient single binocular vision in primary position and down reading gaze, but to maximize the area of binocularity. At times, it may be impossible to improve the overall excursion of an eye with limited eye movements, and it is useful to perform surgery on the contralateral eye, limiting its range, but allowing the patient to achieve maximum binocularity.[28,29,30]

A 69-year-old man was evaluated for a three-month history of vertical diplopia. He was found to have 2 mm of right proptosis and marked limitation of elevation of the right eye [Supplementary Figure 9, Supplementary Figure 10]. His only area of binocularity was in extreme down gaze [Supplementary Figure 11]. Orbital CT demonstrated enlargement of the inferior rectus muscles, compatible with thyroid eye disease. Recession of the right inferior rectus muscle might have provided single binocular vision in primary gaze, but would very likely lead to diplopia in down gaze. Instead, inferior oblique surgery on the left eye was performed [Supplementary Figure 12], which dramatically improved the patient's area of single binocular vision [Supplementary Figure 13, Supplementary Figure 14].

A 36-year-old woman was referred for evaluation of double vision. She was known to have fibrous dysplasia of the left orbital roof. Previous cranial reconstructive surgery had left her with restriction of the left superior rectus muscle [Supplementary Figure 15], making it difficult for her to look down [Supplementary Figure 16, Supplementary Figure 17]. Because I realized that it would not be possible to make her left eye move better, I performed a right inferior rectus recession with posterior fixation suture (Faden procedure) [Supplementary Figure 18]. This, combined with a left superior rectus recession, reduced her diplopia while reading and achieved single binocular vision in primary gaze as well [Supplementary Figure 19, Supplementary Figure 20].

Although many of us spend little time in the operating room, there are some procedures that traditionally have fallen within the purview of neuro-ophthalmology. One such example is optic nerve sheath fenestration. [31,32]

A 34-year-old woman reported that things “look dark.” Her visual acuity was 20/30, right eye, and 20/50, left eye, with bilateral papilledema. She was found to have a tuberculum sellae meningioma [Supplementary Figure 21], but in spite of neurosurgical resection, her papilledema persisted and her visual fields became more constricted [Supplementary Figure 22]. She underwent a right optic nerve sheath fenestration, and within one week, she noted improvement in her visual function. At two years follow-up, her bilateral optic disc edema had resolved, and while she was left with optic atrophy [Supplementary Figure 23] and arcuate nerve fiber bundle defects in her visual fields [Supplementary Figure 24], central acuity was preserved at 20/25 in each eye.
The mechanism of action and indications for optic nerve sheath fenestration remain unclear. Non-controlled studies suggest that it can protect the optic nerve from progressive damage related to intracranial hypertension. [33,34] Although generally accepted as a treatment for chronic papilledema secondary to idiopathic intracranial hypertension, [35,36] there are no controlled prospective studies evaluating appropriate surgical indication and timing, and progressive visual loss may occur even following optic nerve sheath fenestration surgery. [37]

**How the Neuro-ophthalmologist Can Assist with Treatment**

The past thirty years have seen a revolution in the endovascular approach to a variety of intracranial lesions, including aneurysm and arteriovenous malformation. [38] While transarterial embolization has been largely replaced by transvenous access sometimes a neuro-ophthalmologist may assist with a transorbital approach. [39,40,41] A 61-year-old woman reported the acute onset of blurred vision in each eye, and an eye examination was unremarkable. While her symptoms resolved, one month later, she complained of double vision. A CT and MRI of the brain were reported as normal. One month later, she developed pulsatile tinnitus and over the next three months, her diplopia worsened, and she developed bilateral conjunctival injection. The patient was started on systemic antibiotics, but when her vision deteriorated, she was referred for neuro-ophthalmic evaluation [Supplementary Figure 25].

At the time of examination, her visual acuity was 20/25, right eye, and 20/400, left eye with marked visual field abnormalities. There was a 1.2 log, left relative afferent pupillary defect, with bilateral abduction deficits, 2mm of left proptosis with marked chemosis of the left eye. The right fundus was normal while the left showed prominence of the retinal veins. Cerebral angiography confirmed a carotid-cavernous sinus fistula [Supplementary Figure 26], with cortical venous hypertension. A transvenous approach through the inferior petrosal sinus to embolize the fistula was unsuccessful. I was able to assist in accessing the fistula through the right superior ophthalmic vein [Supplementary Figure 27]. The neuroradiology team was able to use detachable coils to embolize the fistula [Supplementary Figure 28], with resolution of chemosis [Supplementary Figure 29] and diplopia, and improvement in visual acuity.

When the proximal superior ophthalmic vein is atretic or thrombosed the cavernous sinus may be accessed directly by navigating a needle through the superior orbital fissure. [42,43,44] This 71 year old patient presented with redness, tearing, and pressure sensation on the right. She had limitation in elevation, depression, and adduction [New Fig 30], suggestive of a mild right III and VIth nerve palsies plus [Supplementary Figure 31] arterialization of her episcleral vessels. Her angiogram showed evidence of an extensive carotid cavernous fistula [Supplementary Figure 32]. As in the first case traditional approaches were not available, and she underwent a direct percutaneous puncture through the orbit [Supplementary Figure 33] into the cavernous sinus with embolization of the cavernous carotid fistula. She had complete resolution of redness, return of vision, and improvement in her motility as indicated by quantitative assessment.
How the Neuro-ophthalmologists Can provide advice for a variety of treatment decisions?

Following the observation of J. Lawton Smith, MD, [45] and confirmed by others, not only can radiation therapy slow progression, but it may actually improve visual function in patients with optic nerve sheath meningioma. [46,47,48,49]

A 39-year-old woman presented with a three-year history of decreased vision to 2/200, right eye, while vision in the left eye remained 20/20 [Supplementary Figure 34]. She had a 2.1 log right afferent pupillary defect and evidence of early PM bundle drop out. MRI confirmed the presence of a right optic nerve sheath meningioma [Supplementary Figure 35], and the patient was treated with 50 Gy of fractionated conformal external beam radiation. Three months later her right visual acuity improved to 20/200 [Supplementary Figure 36], she was able to “see colors.” Four years later, her acuity further improved to 20/40 [Supplementary Figure 37]. In a commensurate fashion, the patient’s right relative afferent defect improved from 2.1 log units, to 0.9 log (3 months following radiotherapy) to 0.3 log (4 years following radiotherapy). In our patient, OCT did demonstrate moderate nerve fiber layer thinning (75.22µm average thickness in the affected eye vs. 82.92µm in the unaffected eye) [Supplementary Figure 38]. Peter Savino pointed out in the seventh Hoyt lecture, [50] OCT might help predict which patients are more likely to experience improved visual acuity following treatment. As our patient demonstrates, thinning of the nerve fiber layer does not preclude improvement in central acuity and visual fields.

In linking the neuro-ophthalmics increasing role in treatment with improved methods of quantifying our clinical findings, it will be essential that we obtain Class 1 evidence with prospective, randomized, double-blind clinical trials. To date, we have completed two: the Optic Neuritis Treatment Trial (ONTT) [51] and the Ischemic Optic Neuropathy Decompression Trial (IONDT). [52] Both studies provided useful information concerning therapy, but perhaps more importantly, they have delineated the natural history of these two optic nerve disorders changing many of our preconceived notions. [53,54,55] The ONTT proved that while intravenous corticosteroids might hasten visual recovery early in the clinical course, over a fifteen-year period, there was no difference in recovery of visual function between treated and untreated patients. In fact, oral corticosteroids predispose patients to recurrent attacks of optic neuritis. The ONTT also taught us a great deal about the likelihood of a patient’s developing multiple sclerosis following an episode of optic neuritis, and demonstrated that MRI of the brain is a powerful predictor of the chances of developing demyelinating disease with long-term follow-up. The IONDT proved that optic nerve sheath fenestration was not an efficacious in the treatment of ischemic optic neuropathy but more importantly found that approximately 40 percent of patients (with acuity < 20/60) can experience spontaneous improvement. This 74 year old gentleman presented in December of 1988 with sudden decreased vision. Although acuity was 20/25 and 20/20, he had evidence of an inferior paracentral visual field defect [Supplementary Figure 39] with associated hyperemia and hemorrhages on the inferior aspect of the right disc [Supplementary Figure 40]. He was diagnosed with anterior ischemic optic neuropathy. One month later his vision was worse. Acuity had dropped from 20/25 to 20/200 and although the inferior arcuate defect was unchanged, he now had a new superior arcuate defect [Supplementary Figure 41] corresponding to the localized area of swelling [Supplementary Figure 42]. Progressive AION in 1988 was felt to be unusual. One year later, he returned with a six day history of decreased vision in the left eye. Just like the right, he now had a paracentral defect [Supplementary Figure 43] with evidence of acute edema, hyperemia,
and some telangiectatic vessels affecting the left disc [Supplementary Figure 44]. In a manner similar to the right eye, nine days later vision dropped to 20/50 [Supplementary Figure 45]. He underwent a left optic nerve sheath fenestration as it was suggested this might have a beneficial effect, [56] and his acuity improved from 20/50 to 20/30. Visual acuity had also improved from 20/200 in the right eye to 20/70. It might be possible to conclude that optic nerve sheath fenestration in one eye has a beneficial effect in the other eye. But this improvement in the visual acuity in the right eye had occurred before the fenestration surgery. In spite of improved acuity visual field defects persisted [Supplementary Figure 46].

A third prospective study, the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) is currently underway. Hopefully, it will provide us with a better understanding the natural course of IIH and the efficacy of medical therapy.

*Neuro-ophthalmologists and their surgical colleagues*
I like to teach my residents that there is no operation that can't make a patient worse. Complications and unexpected results are an unfortunately not rare event following therapy. As our neurosurgical and head and neck surgical colleagues become increasingly aggressive (while attempting to be minimally invasive) it is imperative that quantitative assessment be utilized to pre-operatively as well as post operatively to evaluate these patients for pre-existing deficits and new changes. This 37 year old triathlete was referred for intermittent horizontal diplopia and numbness involving his left cheek. A CT scan demonstrated a mass in the left cavernous sinus [Supplementary Figure 47]. In July of 1989 he underwent a pterional craniotomy with extradural resection of the anterior clinoid and excision of a meningioma. Post operatively he had complete ophthalmoplegia. His third nerve gradually recovered but he was left with an incomplete left VIth nerve palsy [Supplementary Figure 48]. In addition he was noted to have an afferent pupillary defect and evidence of a new inferior arcuate visual field defect which also persisted [Supplementary Figure 49].

Unroofing of the optic canal for any reason carries a risk to the optic nerve. [57,58] Surgery in the cavernous sinus also carries a substantial risk for worsening or creating cranial nerve palsies following cavernous sinus surgery. [58] In our experience the most common cause of clinically significant optic neuropathy in fibrous dysplasia is surgery. [59,60,61]

In conclusion, I see neuro-ophthalmology evolving, not only in our ability to establish the correct diagnosis, but becoming more involved in treatment of our patients. It is essential that data regarding anatomy, physiology, and psychophysics be obtained in a standardized and reproducible quantifiable manner. It is this data that allows us to determine whether our patient’s condition is changing and enables us to make better decisions regarding therapy. As neuro-ophthalmologists, we now stand ready to play a more active role in patient evaluation, guiding intervention, and being there to assist when intervention is necessary.

**References**


52. Ischemic Optic Neuropathy Decompression Trial (IONDT) Research Group. Optic nerve decompression surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful. JAMA. 1995;273:625-632.


