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Editorial

The Foundation of Neuro-ophthalmology in the United States of America

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Thinkers have long appreciated that the human eye is a remarkable product of natural engineering. The ability to resolve 1 minute of arc is amazing, but human perception goes beyond the optics to make sense of the inputs; the understanding of that integration is the study of neuro-ophthalmology. Neuro-ophthalmology melds 2 disciplines, neurology and ophthalmology, exploring the link between the eye and the brain. This link begins with the afferent input through the optic nerve, involves complex processing, and includes efferent output to control the pupil and eye movements. Where did neuro-ophthalmology begin? In this article, we briefly consider the evolution of neuro-ophthalmology from the ancient Greeks to modern times, with a recognized bias for American giants in the field. Much of this derives from a presentation given at the 150th American Ophthalmology Society (AOS) Annual Meeting by one of the authors (A.A.S.).

From the Ancients to the Early 20th Century

Neuro-ophthalmology melds two disciplines, neurology and ophthalmology, exploring the link between the eye and the brain.

It can be argued that Socrates (469−399 BCE) was a neuro-ophthalmologist. In "Allegory of the Cave" from *The Republic*, he recognized that we cannot trust the senses and that filters of the mind alter perception.[1] This presaged our modern understanding of visual perception involving the primary and associated visual cortex that abstracts visual information, allowing extraction and amplification of the desired information and filtering out of "noise." Socrates did not directly document his thoughts and philosophies. That role fell to his student Plato (427−347 BCE), whose writings provide us with insights into the thoughts of the ancient Greeks.[1]

Plato also became the proponent of one of the first theories of vision, the emission theory.[2] This theory professed that the eye was not only a receptor, but also an emitter, with finger-like projections reaching out to touch the environment. Plato's student Aristotle (384−322 BCE) argued that the small eye could not project its emission to distant mountains.

The emission theory survived and gained mathematical credence from Euclid (325−265 BCE), who provided some of the first optical ray tracing in reversal as the rays emanating from the eye.[3] At the same time, Herophilus (344−280 BCE) linked the eye with the brain, describing the optic nerve and chiasm.[4]

The efferent connections between the brain and the eyes were not described until Galen of Pergamon (130−200 CE) did so. Galen noted cranial nerves III, IV, and VI and, learning from the injuries of gladiators, connected anatomy and physiology.[5] Galen also agreed with the emission theory in deference to authority, but added that images were perceived through the resonance of light with the extramission from the eyes. Galen reasoned that the hollow optic nerves carried resonating waves to the ventricles of the brain. He described the ventricles as 3 cavities that corresponded to perception at the front ventricle (closest to the eye), reasoning at the middle ventricle, and memory at the back ventricle. This theory of consciousness survived for more than a century and can be found in the earlier drawings of Leonardo Da Vinci (1452−1519 CE). However, reality trumped authority in Da Vinci's later work. He eventually developed a deep understanding of anatomy, with drawings that illustrated both lateral ventricles and the passageways to the third and fourth ventricles.[6] Vesalius (1514−1565 CE) corrected Galen's impression that the optic nerves were hollow and showed the true anatomy, with the optic nerves terminating at the thalamus.[7]

The Early Modern Europeans expanded on the basic neuro-ophthalmic anatomy developed during the Renaissance. Thomas Willis (1621−1704 CE) and William Briggs (1650−1704 CE) showed that the eyes provided input to the brain through the optic nerves.[8,9] Marie Flourens (1794−1867 CE) took this one step further and with animal experiments showed that ablating the visual cortex resulted in loss of vision.[10]

By the 19th century, our understanding of the anatomy of the brain was propelled forward through the work of luminaries including Pierre Gratiolet (1815−1865 CE), who showed by careful dissection that the Gratiolet radiations (optic tracts) were connected to the lateral geniculate nucleus and pretectum[11]; Francesco Gennari (1752−1797 CE), who identified the extra layer in the visual cortex that bears his name (Stripe of Gennari)[12]; Paul Broca (1824−1880 CE), who correlated the anatomic and functional areas of the brain[13,14]; and Hughlings Jackson (1831−1911 CE) and Hermann Wilbrand (1851−1935 CE), who understood structure and function from detailed clinical descriptions with pathologic correlations.[15,16]

Wilibrand's 9 classical volumes, *Neurologie des Auges* (*The Neurology of the Eye: A Handbook for Neurologists and Ophthalmologists*), cowritten with Alfred Saenger, led to the foundation of neuro-ophthalmology as we know it.[16] Wilibrand was the first to document that homonymous hemianopia could occur as a result of any postchiasmal

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lesion, from the optic tracts to the occipital cortex. Concurrently, Johann Freidrich Horner (1834−1886 CE), in Zurich, together with the French physiologist Claude Bernard (1813−1878 CE), described sympathetic denervation of the eye in what we now know as Horner's syndrome.[17] However, the anatomic understanding of the retina and its outputs was left largely to the father of modern neuroscience, the Spanish scientist Santiago Ramon y Cajal (1852−1934 CE). Using a primitive light microscope, Cajal was able to draw in exquisite detail the structure of the brain and the retina on a cellular level.[18,19] This work led to him being awarded the Nobel Prize in Physiology and Medicine in 1906.[20]

The German physiologist Hermann von Helmholtz (1821−1894 CE) gave us a way to look at the eye in vivo with the ophthalmoscope.[21] The ability to see the living eye led to a great leap in understanding of the interplay between the eye and the brain. One of the giants who made the best use of Helmholtz's discovery was Albrecht von Graefe (1828−1894 CE), who contributed to all facets of ophthalmology, including neuro-ophthalmology. For example, he was the first to detect bilateral papilledema in patients with brain tumors.[22,23] His cousin Alfred Graefe (1830−1899 CE) concentrated on the efferent system and strabismus and, along with the Dutch ophthalmologist Frans Cornelius Donders (1818−1889 CE), provided unifying theories on strabismus, convergence, and accommodation. But it was 2 Americans in Philadelphia, William C. Posey (1866−1934 CE) and William C. Spiller (1863−1940 CE), who coedited the book *The Eye and the Nervous System*, who set the literary foundation and tradition for American neuro-ophthalmology.[24]

The Start of the American Ophthalmology Society

However, the earliest roots of neuro-ophthalmology in North America can be dated to around the time of the founding of the AOS in 1864.[25] This was the same year of the United States Civil War battle of Chancellorsville, and there followed a description of a case of what would be later known as Horner's syndrome. A soldier who was shot in the neck demonstrated ptosis, miosis, and anhidrosis as reported by 3 field medics, Mitchell, Morehouse, and Keen.[26]

The teachings of neuro-ophthalmology soon became part of the teachings of the AOS. In 1938, P. J. Leinfelder at the University of Iowa published his AOS thesis, "Optic Atrophy after Lesions to the Optic Tract." Some of Leinfelder's compatriots became synonymous with neuro-ophthalmology. Most prominent of these is fellow AOS member and past president (1965) Frank Burton Walsh (1895−1978).

The New World

Walsh, transplant to the United States from Canada, usually is credited with founding the modern field of neuro-ophthalmology.[27] Born in Saskatchewan, Canada, his formal education at Queen's University at Kingston was interrupted by World War I, yet despite injury at Ypres, he returned to complete his Doctor of Medicine degree at the University of Manitoba in 1921. He worked as a general practitioner in Saskatchewan for 9 years and then decided to specialize in ophthalmology. Going straight to the top, he wrote to Dr. Wilmer at the newly opened Wilmer Eye Institute at Johns Hopkins University requesting a position as a resident in 1930. During his time at Wilmer, Walsh served as chief resident and worked with the neurologist Frank Ford, who was writing a book. Walsh went on, in 1934, to become a member of the staff at Wilmer. Professor Walsh played a seminal role in establishing neuro-ophthalmology as a specialty in its own right. His book *Clinical Neuro-ophthalmology*, published in 1947, is seminal in the field.

The world of neuro-ophthalmology developed some momentum as illustrated in 1950 by the *Annual Reviews of Neuro-Ophthalmology*, written by C. Wilbur Rucker (1904−1986) at the Mayo Clinic.[28] Rucker reviewed the neuro-ophthalmologic literature published between 1950 and 1952.[28,29] He gave coherence to a field from what was before a series of unrelated and unexplained clinical descriptions.

Soon after, in 1958, Walsh approached his ophthalmology fellow William (Bill) F. Hoyt (born 1926) and asked him to help write the third edition of what we now call *Walsh and Hoyt's Clinical Neuro-Ophthalmology* (1969). This book expanded to 3 volumes and became the bible of neuro-ophthalmology. This legacy continued in the form of subsequent editions edited by Neil R. Miller and Nancy J. Newman.

To date, the acme of neuro-ophthalmology remains Bill Hoyt. He trained at the University of California, San Francisco, and completed a Fulbright fellowship in Vienna. Hoyt considers his greatest legacy to be the training of more than 72 neuro-ophthalmology fellows, many of whom have become teachers and mentors themselves in neuro-ophthalmology.

Walsh and Hoyt had one particularly important contemporary, David Glendenning Cogan (1908−1993), who received his MD from Harvard and completed an ophthalmology residency at the Massachusetts Eye and Ear Infirmary. Cogan, who succeeded Verhoeff as the director of Harvard's Howe Laboratory, published his own 2 treatises *Neurology of Ocular Muscles* (1948) and *Neurology of the Visual System* (1966). Cogan sought to combine the clinical and basic sciences first at the Howe Laboratories and later at the National Eye Institute.

Cogan helped train J. Lawton-Smith (1929−2011), who brought a religious fervor and a great sense of humor to neuro-ophthalmology. Lawton-Smith fulfilled his residency training at Wilmer with Walsh and became enthralled with neuro-ophthalmology. On later completing his fellowship with Cogan, Lawton-Smith returned to Duke, and then worked at the Bascom Palmer Eye Institute. Lawton-Smith published more than 335 articles, books, and editorials and described more than 20 completely novel entities.[30] Lawton-Smith was joined at Bascom Palmer by several

notable neuro-ophthalmologists, including Nobel "Nobby" David (born 1927), Joel Glaser (1938–2011), and later Norman J. Schatz (born 1936), and their group turned South Florida into a powerhouse of neuro-ophthalmology.

A prodigy of Hoyt, Glaser published his own highly acclaimed textbook on neuro-ophthalmology, revised and published as a third edition in 1999.[31] Glaser had a legendary bond to Schatz. The two would regularly put on neuro-ophthalmology teaching as a comedy act with Glaser playing the straight man.

In the meantime, Simmons Lessell (born 1933) also used the connection of humor and neuro-ophthalmology as part of his approach for extraordinary teaching first at Boston University and then at Harvard. The "gaon" of neuro-ophthalmology, Lessell combined training in neurology and ophthalmology, which was reflected in his own celebrated teaching style.[32] Lessell is reported to have asked Cogan where he should serve his fellowship, to which Cogan replied, "A neuro-ophthalmologist is someone who other people think is a neuro-ophthalmologist… you don't need a fellowship."[32] Lessell has published well over 200 articles, including seminal descriptions of toxic optic neuropathy, cerebral achromatopsia, palinopsia, indirect optic nerve trauma, and pachymeningitis.

Lessell joined a distinguished group in 2003 when he was awarded the joint American Academy of Ophthalmology/North American Neuro-Ophthalmology Society Hoyt Award. This award is appropriately named after the father of modern neuro-ophthalmology, William F. Hoyt. Another prominent Hoyt awardee is Jonathan D. Trobe. A teacher of teachers himself, Trobe has authored the Legacy series in the *Journal of Neuro-ophthalmology*, which highlights the accomplishments of the founders of neuro-ophthalmology in America. The full list of the 14 Hoyt award winners is seen in Table 1. Stan Thompson, the 2002 winner of the Hoyt Award, helped summarize 20th-century American neuro-ophthalmology.[24] He mentioned many American neuro-ophthalmologists, including Ronald M. Burde, James J. Corbett, Robert B. Daroff, and Peter Savino, that the present short review is too limited to cover.

It is on the basis of this foundation that neuro-ophthalmology flourishes today. The teachers of the teachers have left us with a legacy of their fellows, many of whom populate the list of Hoyt Awardees. Steve Feldon, Anthony Arnold, and Nancy Newman, all past presidents of the North American Neuro-Ophthalmology Society, have made wonderful contributions to our understanding of optic neuropathy, optic nerve drusen, and diagnostic approaches, respectively. Neil Miller has continued the legacy of Walsh at Wilmer, publishing extensively and advancing our understanding of neuro-ophthalmological diseases. Sohan Hayreh furthered our understanding of ischemic optic neuropathies. Jonathan Horton combined neuroscience and imaging technologies to delineate cortical anatomy and physiology. Mark Kupersmith has made important contributions to our understanding of ocular myasthenia gravis. Len Levin has taught us a great deal about what factors influence the life and death of retinal ganglion cells and their axons in the optic nerve. These leaders have used different approaches and investigational methods, but it has been the constants of careful observation, deep thinking, and integration of various disciplines that define neuro-ophthalmology today.

We stand at the cusp of a new era when genetics, molecular biology, and, most of all, scientific approaches will shift the paradigm from phenomenology to hypothesis testing. And as always, neuro-ophthalmology will be appreciated as an exceptional system through which to understand the brain.

Table 1. William F. Hoyt Award Recipients

Year	Recipient
2001	Thomas J. Carlow, MD
2002	H. Stanley Thompson, MD
2003	Simmons Lessell, MD
2004	Creig Hoyt, MD
2005	Neil R. Miller, MD
2007	Joel S. Glaser, MD
2008	Peter J. Savino, MD
2009	Norman J. Schatz, MD
2010	Jonathan Trobe, MD
2011	Steven A. Newman, MD
2012	Alfredo A. Sadun, MD, PhD
2013	Nancy J. Newman, MD
2014	Mark J. Kupersmith, MD
2015	Anthony Arnold, MD

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