Editorial

Ophthalmic Pathology: History, Accomplishments, Challenges, and Goals
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The historical part of this editorial is based in part on The History of Ophthalmology. During the 16th and 17th centuries, physicians were considered academicians and surgeons were considered craftsmen; barbers were technicians and disease was thought to be due to morbid humors. The printing press was invented, and Bartisch’s Ophthalmomodouleia was the first comprehensive ophthalmology textbook. Pathology was determined by gross inspection of tissues; during this time, Morgagni described the gross appearance of cataracts. Ophthalmology was established as a specialty in Europe during the 17th and 18th centuries. George Joseph Beer established ophthalmology as a specialty in Vienna; Beer had studied under Joseph Barth and was the founder of the first ophthalmologic school and clinic in Europe.

The first important theme in ophthalmic pathology is the importance of individuals in advancing the field. One such individual was James Wardrop, who studied under John Hunter and George Beer. Wardrop was a Scottish surgeon who specialized in eye surgery and wrote Morbid Anatomy of the Human Eye. He described retinoblastoma, known then as “fungus hematodes,” as a distinct entity, and described the first well-documented case of metastatic uveal melanoma. We continue to study the molecular mechanisms of these 2 tumors today.

The second important theme in ophthalmic pathology is the confluence of technology. The invention of the ophthalmoscope by Hermann von Helmholtz in Heidelberg in 1851, along with the concept of cellular pathology as developed by Rudolph Virchow in Berlin in 1858, enabled correlation of cellular pathology of the eye with clinical image assessment of the fundus. This concept runs through to today; for instance, the Müller cells named after Heinrich Müller in Würzburg may be identified by confocal scanning laser microscopy; Henle’s layer described in the 1800s by Jacob Henle may be seen by posterior segment ocular coherence tomography; and Bowman’s layer described by Sir William Bowman may be demonstrated by corneal ocular coherence tomography.

During the 1800s, ophthalmic pathology continued to develop in England. Moorfields Eye Hospital, created after the English evacuation of Egypt, was established in 1805. At Moorfields, ophthalmologists and morbid anatomists advanced the field, including John Dalrymple, Sir William Bowman, Edward Nettleship (who established the tradition of the ophthalmic pathologist serving as the curator/librarian), Edward Treacher Collins, Sir John Parsons, and George Coats, who described Coats’ disease. In a very real way, ophthalmic pathology enabled ophthalmology to become a medical and surgical specialty. Then came the father of modern ophthalmic pathology, Ernst Fuchs of Vienna. Fuchs’ genius came from his ability to distill critical and key clinical and pathologic features from his extremely busy practice; he saw 20,000 patients per year. He was able to correlate the ophthalmic appearance and histopathologic features of the enucleated eye, for instance, in his description of sarcom des uvealectrus (uveal melanoma). This is the third important theme in ophthalmic pathology: research/clinicopathologic correlation. One should remember that the histologic figures in those days were hand drawn. One can see how beautiful and accurate these drawings are by the example in Figure 1, which shows hand-drawn examples of the microscopic appearance of retinoblastoma done by Wintersteiner compared with examples I photographed in my laboratory.

As Fuchs was the founder of modern ophthalmic pathology, Frederick Verhoeff, an American Ophthalmological Society (AOS) member, was the founder of American ophthalmic pathology. Verhoeff was in the third graduating class of the Johns Hopkins School of Medicine and the first ophthalmologist to graduate from Hopkins. He studied under Fuchs, Haab, and Parsons. Verhoeff did it all. At the Massachusetts Eye and Ear Infirmary, he saw patients, performed surgery, prepared pathology slides, did the photography, and typed the pathology reports. He would do well in today’s era of cost containment. Figure 2 shows an image of Verhoeff in his laboratory. Up to this point, eye pathology was more or less a hobby of interested ophthalmologists who assembled together and exchanged and described interesting cases. Verhoeff’s influence created an environment that enabled legitimizing ophthalmic pathology and its importance to ophthalmology. This led to the so-called Golden Age of Eye Pathology. This was the era when ophthalmic pathology entered into the realm of pathologists and ophthalmic pathology became a viable career. The leaders in this era were Norman Ashton in England and Lorenz Zimmerman at the Armed Forces Institute of Pathology (AFIP).

Norman Ashton was a pathologist by training. He practiced at the Institute of Ophthalmology in London and was a consummate histopathologist and experimental pathologist who unraveled the pathogenesis of a variety of ophthalmic disorders. His work was the forerunner of modern diagnostic and experimental ophthalmic pathology. On the other
side of the pond was Lorenz Zimmerman. Dr. Zimmerman, an infectious disease pathologist by interest, inherited the treasure trove of backlogged eye pathology cases at the AFIP in the 1950s. During the peak of his career, in the 1960s through the mid-1980s, he and his trainees described the histopathologic features of most major ophthalmic conditions. The importance of his work cannot be overstated, especially with regard to his talent as a teacher. At the height of Verhoeff’s career and before Zimmerman’s arrival on the scene, there were enough ophthalmologists interested in ophthalmic pathology to form an ophthalmic pathology club. The first meeting of the Ophthalmic Pathology Club took place at the Army Institute of Pathology in 1947 (Fig 3). These meetings continued at the AFIP for many years; the Ophthalmic Pathology Club became the Verhoeff Society in 1964. Of note is that one of the ophthalmic pathology club members was Georgiana Theobald, who became the first female member of the AOS in 1934.

In 1998, the Verhoeff Society became the Verhoeff-Zimmerman Society. The motto of the society is ex errato lux (we learn from our mistakes) (Fig 4). Verhoeff was an AOS member, and Zimmerman was an honorary AOS member; both were Howe Medal recipients. Ophthalmic pathology had added value to the practice of ophthalmology by structurally defining and understanding ophthalmic disease processes, which in turn led to medical and surgical treatments. The 3 important themes in the ophthalmic pathology story continued: confluence of technologies, person-driven laboratories, and research/clinicopathologic correlation.

From the 1960s to the 1980s, the confluences of technologies were light microscopy, electron microscopy, and immunohistochemistry; the field was person driven by the students of Ashton or Zimmerman; research/clinicopathologic

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**Figure 1.** Comparison of hand drawings and photomicrographs of retinoblastoma. **Upper left and lower left:** Drawings of retinoblastoma histology made by Wintersteiner (from Wintersteiner H. Das Neuroepithelioma Retinae. Eine anatomiische und klinische Studie. Vienna: Franz Dueticke; 1897).**Upper and lower right:** Images of histology of retinoblastoma (hematoxylin–eosin, original magnification ×10 and ×25).

**Figure 2.** Frederick Verhoeff, MD, at the microscope. Note that he was smoking and not using gloves, 2 relics of the past.
correlation flourished; and there was a proliferation of small departmental laboratories and a trend for dual board certification in ophthalmology and pathology for directors of larger laboratories. From the 1990s to the present, there have been changes in how ophthalmic pathology is practiced, largely due to decreased reimbursements along with managed care and the recent Affordable Care Act. There were a series of articles and editorials published about this. There were numerous other factors that led to changes in practice, including few candidates for ophthalmic pathology training, a lengthy training time, the highly competitive nature of National Institutes of Health funding, and a lack of fully supported faculty positions. At the time of Norman Ashton’s death, William Spencer noted these realities in his 2001 editorial “Ophthalmic Pathology at the Crossroads.” He challenged the leaders in ophthalmology to step forward and address the potential consequences of these changes. Zimmerman noted that “It would be accurate to say that the field was regressing to the way it was in the United States before World War II.” In many ways, Zimmerman was correct. A handful of regional ophthalmic pathology laboratories flourished. The AFIP was a victim of its own success; its trainees were heading ophthalmic pathology laboratories across the United States, and the AFIP eventually closed its doors in 2010.

David Apple presented a paper at the 2003 AOS meeting entitled “The Demise of Diagnostic Ocular Pathology: Temporary or Forever?” I would argue that this was a temporary situation. Ophthalmic pathologists noted that changes needed to be made. They knew that (1) our specialty added value to ophthalmology, including from research/clinicopathologic correlation; (2) dedicated individuals advanced the field; and (3) ophthalmic pathology advances involved a confluence of technologies, just as it always has been. We then recognized that the current confluence of technologies are digital technology and molecular biology. In a strengths, weaknesses, opportunities, and threats analysis in 2006, the American Association of Ophthalmic Pathologists recognized the importance of these newer technologies and the benefits of coupling our specialty with another clinical specialty, namely, ocular oncology, because there was so much overlap and a number of ophthalmologists are trained in both.

Figure 3. First meeting of the Ophthalmic Pathology Club. Army Institute of Pathology, 1947, Washington, DC.

Figure 4. Verhoeff-Zimmerman Society coat of arms. Note the microscope at the top, 2 hands fighting about a glass slide, 3 X’s denoting the 3 originators of the society (Ted Sanders, John McLean, and Benjamin Rones), slide of uveal melanoma, microscope, and motto “Ex Errato Lux” (we learn from our mistakes).
In regard to digital technology, several Internet-based eye pathology teaching programs have been developed, such as the Internet-Based Eye Pathology Teaching Initiative in my department and Virtual EyePath slides using Aperio technology (Aperio, Leica Biosystems, Buffalo Grove, IL), which is available at the American Association of Ophthalmic Oncologists and Pathologists website.6

Molecular biology and molecular pathology have played a major role in contemporary ophthalmic pathology, with recent articles describing gene expression profiling in uveal melanoma9 and retinoblastoma.10 Examples of combinations of digital technology and molecular biology in ophthalmic pathology include polymerase chain reaction, flow cytometry, Western blots, confocal scanning laser microscopy, and others.

In 2012, the American Association of Ophthalmic Pathologists became the American Association of Ophthalmic Oncologists and Pathologists. Our field now has a journal of its own, Ocular Oncology and Pathology, and the first issue was published this year.11 The first Oncology/Pathology Subspecialty Day occurred at the 2014 American Academy of Ophthalmology annual meeting in Chicago. The Verhoeff-Zimmerman Society is alive and well. We continue to meet annually at locations around the United States; we bring in talented new ophthalmic pathologists who are the future of our specialty; and, yes, there are modern day Verhoeffs and Zimmermans among us, using today’s technology to advance our field. These experts are passionate about the study of ophthalmic disease and experts in its pathologic diagnosis.

Ophthalmic pathology has a rich heritage in ophthalmology. Ophthalmic pathology helped ophthalmology become the medical/surgical specialty that it is today. Individuals have advanced and continue to advance the field; these advances occur because of confluences of technologies. Expertise in ophthalmic pathology is essential for clinicopathologic correlations and ophthalmic research. Ophthalmic pathology will thrive if it continues to be an integral part of ophthalmology.

References


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