In memoriam: Frederick A. Jakobiec, M.D., D.Sc., the “king of cysts,” and so much more

In late 2020, the fields of ophthalmology and ophthalmic pathology lost a passionate and witty teacher and scholar, an eloquent speaker and writer, and a brilliant diagnostician and observer, who dedicated his life to the study of the eye, Dr. Frederick A. Jakobiec, also known as “FAJ,” “Dr. J,” and “Fred” [Figure 1]. It was because of his unsolicited recommendation (something he tended to do), that I ended up as his chosen successor and the Director of the Cogan Eye Pathology Laboratory at Massachusetts Eye and Ear (MEE). He always spoke fondly of his own teachers – from the priests at his Catholic elementary school to father of ophthalmic pathology, Dr. Zimmerman, at the Armed Forces Institute of Pathology, and in turn, championed his mentees. I was lucky to be among those he shared meals with at Legal Sea Foods in Boston, where he always encouraged dessert (he had quite a sweet tooth), and someone he would call at 10 pm on a weekday to share his excitement about an interesting case. Once he considered you a trusted friend and colleague, he would make Polish jokes (his father was Polish), let his colorful sense of humor emerge and discuss news, politics, and departmental gossip, quietly of course.

A frugal saver and wise investor, he amassed and left quite a fortune in support of the places he valued so much, including, but not limited to, the Harvard College History of Science Department, Columbia University, where he trained in ophthalmology and anatomic pathology, and MEE. Perhaps the five cents in change he always insisted I give him after going to get us coffee added up over time. He loved libraries, and with one of his gifts, ensured that the MEE library, where he would sprawl out across the large wooden tables to manually organize the references for his many written works, would stand the test of time in the electronic era. Dr. Jakobiec was never interested in using a computer or the internet and e‑mail, and was, for lack of a better term, “technologically challenged.” His trainees all became quite adept at interpreting his cursive longhand and he would bring stacks of lined paper filled with his musings and covered in coffee into the laboratory from home. Near the end of this life, he did finally embrace the concept of Uber to easily shuttle him to and from work, as he never drove, and he learned to use a microwave.

Although he was certainly in part drawn to ophthalmology because his beloved younger brother, Thaddeus, was blind from complications of retinopathy of prematurity, Dr. Jakobiec was also a true anatomic pathologist. He applied the principles of particularly dermatopathology, hematopathology, and soft‑tissue pathology to the unique environment of the eye and ocular adnexa, and he knew and described when such established principles did not quite fit. His contributions to ophthalmic pathology were vast and varied. He bridged the words of diagnostic surgical pathology and ophthalmology, choosing to publish most of his work in the ophthalmologic literature in order to share his love and understanding of pathology with his clinical colleagues. Other pathologists would say that he did not sign out a case without also publishing it. Meaning, Dr. Jakobiec would turn unusual examples of histopathologic phenomena that he encountered during sign‑out (occurring in the eye or ocular adnexa) into literary treatises with musings on differential diagnosis, histogenesis, and new insights into the disease entity. He certainly had his favorite topics and least favorite tissues and would sometimes sigh at the sight of a stack of slide trays containing non‑neoplastic corneas. Still, only he could make medical corneal pathology fun and original, characterizing and beautifully illustrating retrocorneal fibrous membranes, for example.[1] Summarizing his work (which encompasses over 500 original articles) would take volumes of text, so I have chosen to highlight a select few of his favorite contributions to the field of eye pathology that I find particularly useful, from my perspective as one of his last fellows.

The adnexal structures of the skin and the cysts and tumors that arise from them fascinated Dr. Jakobiec. He described himself as the self‑crowned “king of cysts,” having published over 40 articles, starting in 1978,[2] on a variety of ocular adnexal (conjunctival, orbital, and eyelid skin) cysts. He outlined the immunophenotypes of the cyst linings and postulated the histogenesis of each. One of his favorite cysts, and probably the most clinically important to characterize and appropriately diagnose, was the lesion he termed “intratarsal keratinous cyst” [Figure 2].[3] The previously poorly defined entity is important because it may mimic chalazion (clinically) or epidermoid cyst (histologically) but should be treated differently than either of those conditions. Intratarsal keratinous cyst is derived from the Meibomian gland duct and should be excised en bloc to avoid multiple recurrences, rather than undergo curettage or marsupialization, as would be the case with the latter two entities, respectively. Dr. Jakobiec believed strongly that eccrine glands were not present at the eyelid margin or in the pretarsal eyelid skin and that hidrocystomas (a very common lesion to arise in this location) were nearly all apocrine in nature. He convincingly demonstrated this fact in a 15‑page American Journal of Ophthalmology paper with five figures and several tables detailing the immunohistochemical (IHC) profile of apocrine hidrocystomas and reviewing the normal pilosebaceous-apocrine unit for ophthalmologists.[4]
In addition to those of cysts, Dr. Jakobiec described and was fascinated by the cytokeratin profiles of various specific epithelia. Importantly, in addition to the normal immunophenotype of various ocular and ocular adnexal structures, he described the frequent loss of keratin 7, which is expressed in normal conjunctival epithelium and benign squamous papillomas, in conjunctival dysplasias, which gain expression of keratin 14 and 17 outside of the conjunctival epithelial basal cells.\[5\] Ocular surface squamous neoplasia takes on a variety of morphologic appearances and can overlap with reactive squamous changes, so these adjunct tools may be helpful.

Sebaceous neoplasms were another favorite of Dr. Jakobiec’s. In the 1970s and 1980s, he reported unusual periocular sebaceous tumors in patients with Muir-Torre syndrome, before and after the syndrome had an official name.\[6,7\] He described the treatment of intraepithelial spread of sebaceous carcinoma (SC) with cryotherapy to avoid exenteration.\[8\] Later in his career, after his return from a prolonged medical leave, he revisited the subject with a modern twist, describing novel IHC stains to help distinguish periocular SC from basal cell carcinoma or squamous cell carcinoma with clear cell features [Figure 3].\[9\] He published several unusual architectural patterns of SC as well as the utility of nuclear IHC stains such as p16 and androgen receptor for the detection of subtle pagetoid spread on tiny conjunctival map biopsies.\[10,11\] Adapting and incorporating more modern ancillary testing, with the help of his fellows, he also showed p16 positivity was unrelated to human papillomavirus infection in SC and that many SCs showed high expression of programmed death ligand 1, suggesting the possibility of immune checkpoint inhibition as therapy for locally aggressive or metastatic SC.\[12,13\]

Conjunctival melanocytic neoplasia, including nevi, melanoma and premalignant melanocytic proliferations, was another of Dr. Jakobiec’s longstanding interests. Spanning the course of 40 years, he studied the treatment,\[14\] the ultrastructure (the topic of his American Ophthalmological Society thesis)\[15\] and the immunophenotype of conjunctival melanoma and its precursors.\[16\] He described the features of benign nevi and how the principles of banality are similar to and different from cutaneous melanocytic nevi, as well as which unusual variants of benign melanocytic tumors also occur on the ocular surface. In particular, he noted the common phenomenon of a robust inflammatory infiltrate in entirely benign nevi of adolescents, often a concerning feature in cutaneous melanocytic tumors, and the applicability of HMB-45 gradient staining (as is seen in benign cutaneous nevi) to conjunctival nevi.\[16,17\] One of his final editorial pieces introduced a new terminology to better describe atypical lentiginous and nested junctional conjunctival melanocytic precursor proliferations in a manner that more accurately described the histopathology than “primary acquired melanosis.”\[18\]

Although a bit outside of the world of ocular adnexal tumors and oculoplastic and reconstructive surgery, where many of Dr. Jakobiec’s interests were centered, I would be remiss to not mention one intraocular tumor. In 1975, Dr. Jakobiec described the ultrastructure of medulloepithelioma [Figure 4].\[19\] A
lifelong learner, 40 years later, he used that tumor to learn about the principles of modern molecular genetics and next-generation sequencing. With a variety of trainees and in collaboration with neuropathologists, he produced a series of papers describing the differences and similarities in the immunoreactivity and mutational landscape of intraocular and central nervous system (CNS) medulloepitheliomas, the latter of which is now subsumed under the category of embryonal tumors with multilayered rosettes. Although both tumors show IHC positivity for LIN28A (a newer and helpful marker in the distinction from retinoblastoma in small biopsies), intraocular tumors did not show amplification of the C19MC microRNA locus that characterizes CNS medulloepitheliomas. The clinical observation that intraocular medulloepithelioma was nearly always cured by enucleation but the CNS tumors were often fatal was finally supported by his findings; the two entities, although morphologically quite similar, are cytogenetically and epigenetically different tumors.

Finally, Dr. Jakobeic’s initial work in the field of ocular adnexal lymphomas and lymphoid hyperplasias was seminal. The findings he presented through analysis of hundreds of cases with Dr. Knowles, outlined the key principles of ocular adnexal lymphoid disorders that are now taught as the most basic of facts, at a time when the fields of immunohistochemistry and early molecular genetic pathology were only just emerging. Namely, that (1) nearly all orbital lymphomas are low-grade, “small-cell” lymphomas of B-cell origin, (2) that lymphomas of the conjunctiva are less likely to show systemic involvement that those of the orbit and eyelid skin, likely, we now know, because of the histologic subtype, and that (3) reactive hyperplasia more closely recapitulates the T: B cell ratio of reactive conditions involving lymph nodes (i.e., they are quite B-cell rich as opposed to, for example, those in the skin).

The Mark Twain quote, “Find a job you enjoy doing, and you will never have to work a day in your life,” although excessively sentimental, seemed to apply to Dr. J. He died in his Boston hospital bed of complications of chronic illness, a nearly finished manuscript covered in hand-written edits at his bedside.

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