4 Herpetic Keratitis: The Genesis of a Career in the Early Days of HSV Keratitis Research

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I met Claes Dohlman for the first time at an antiviral conference in 1963 sponsored by Allergan Pharmaceuticals in Irvine, California. We had both been invited to discuss the first antiviral drug effective against a human virus, herpes simplex. The medication was 5-iodo-2′-deoxyuridine, or IDU. It had initially been reported by Kaufman, Nesburn, and Maloney in 1962 [1], while Herbert Kaufman was an ophthalmology resident at Massachusetts Eye and Ear Infirmary.

Herpes simplex viral keratitis was particularly difficult to treat, as there was no specific antiviral medication effective at that time against herpes or any other viral disease in man. Gunderson in 1936 [2] had reported on the use of iodine solution to treat dendritic keratitis and other forms of herpetic keratitis, and this was one of the more popular treatment options prior to the discovery of IDU. The strong iodine solution, acting as a chemical debriding agent, destroyed the epithelium infected with HSV by dislodging this tissue layer. Iodine also acted as a mild to moderate antiviral agent. Sery had looked at many different chemicals for HSV treatment and had suggested silver nitrate solution [3].

I had become interested in herpetic keratitis in 1961 as a first-year resident at Wills Eye Hospital working with Ted Sery and Irving Leopold, using weak silver nitrate to treat HSV dendritic keratitis. When IDU became available, we treated rabbits infected with herpes simplex virus with IDU drops, and published our results reaffirming Kaufman's earlier observations [4]. Even though a number of publications had shown efficacy of IDU for human herpetic dendritic keratitis, there were very few prospective double-blind studies testing this new therapy. Smith, Kline and French Pharmaceutical Company, the manufacturer of IDU, was located across the street from Wills Eye, and Irving Leopold, our ophthalmologist-in-chief, was able to procure IDU drops and its vehicle (placebo) for such a double-blind study. We found, as did Burns [5], that IDU was significantly more effective than the vehicle. In our study, one physician examined and treated all 100 affected patients, while in the Burns study, 41 physicians treated and evaluated 81 cases.

As a thank-you for attending its conference, Allergan arranged for Claes and me the Sunday after the meeting to visit Disneyland in Anaheim. Claes was not only interested in Disneyland, but particularly what I was going to do after my residency in ophthalmology. Our informal chat while touring that Sunday was my fellowship interview. On July 1, 1964, Jules Baum, John Stanley, Jerry Goldman, and I arrived at the Cornea Service of the Massachusetts Eye and Ear Infirmary. We joined Stuart Brown, already a fellow there for a year, who was working on intralamellar stromal implants with Miguel Refojo and Claes. This was

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the early research on the artificial cornea, or keratoprosthesis (K-Pro). Steve Klyce also joined the group that year to work with Sai Mishima.

My corneal fellowship was extraordinary, making friends and meeting new colleagues who have remained in my life for over 50 years, and participating in science that was always interesting and at times groundbreaking. Sai Mishima and Shu Kitano were doing their research with Claes at the Retina Foundation, while Arthur Boruchoff, Mike Wiedman, and Eva-Lisa Martola were in the clinic with Claes. Bobbie Sweebe, the secretary, was our mother hen. Joining this stellar group for weeks at a time were Bengt Hedbys from Sweden and David Maurice from Stanford. What a remarkable combination of inspired researchers, motivators, and friends! Fortunately for the Massachusetts Eye and Ear Infirmary, this ability to attract unique individuals continues to this day under Reza Dana and his colleagues, including Claes Dohlman at 96.

As a corneal fellow, I began several research projects on the corneal unit of the Retina Foundation, now known as the Schepens Eye Research Institute. My interests however, which had started as a resident at Wills Eye, continued to be with herpetic keratitis. Recurrent herpetic keratitis remained one of the main problems with HSV ocular herpes, even as the discovery of IDU had significantly aided the treatment of superficial ocular herpes [6]. Recurrent HSV ocular disease was the cause of most of the scarring and deep corneal herpetic involvement. How to prevent the recurrence of this disease after the initial corneal infection was the major challenge, as there was no experimental animal model for recurrent herpetic keratitis.

Many similarities were evident between naturally recurring herpetic keratitis in humans and the experimentally induced herpetic keratitis in rabbits. In both rabbits and humans, dendritic epithelial keratitis and corneal anesthesia were seen. Favorable response to antimetabolite drugs such as IDU and deleterious effects to corticosteroids occurred. Disciform keratitis was encountered in both species and circulating antibodies formed after infection with herpes. Most importantly, there was persistence of herpes simplex virus and recurrence of infection with or without keratitis.

I had read about recurrent herpetic encephalitis in mice and rabbits induced by systemic epinephrine and thought we could replicate these findings for herpetic keratitis in rabbits. I was introduced to Sidney Kibrick MD at Boston University, who had collaborated with a prior Dohlman fellow, Bernard Zucker. The encouragement of Dr. Dohlman to work with Dr. Kibrick, even though it required driving daily from the Retina Foundation, where the infected rabbits were housed, to Boston University, where the viral cultures were performed, led to the creation of an experimental animal model for recurrent herpetic keratitis [7]. It was also shown by slit lamp observation and positive cultures that these herpetic recurrences could be repeatedly induced in the same rabbit with epinephrine parenteral stimulation over long periods, up to 8 months [8].

After my corneal fellowship at the Massachusetts Eye and Ear Infirmary, I returned to Wills Eye Hospital in November 1965 to work on the Cornea Service as one of the first geographic full-time physicians employed by the hospital, where Wilfred Fry MD was the head. Herpes simplex viral keratitis at that time was a significant problem and almost five percent of our corneal practice was related to herpetic viruses. Three percent of the corneal transplants done at Wills Eye Hospital were done for the ravages of herpes simplex virus infection.

Despite the proven efficacy of IDU for the treatment of superficial herpetic keratitis, it was not effective in all cases of dendritic keratitis. Toxicity to the IDU drops also became a problem. The dosage regimen for IDU therapy was difficult, requiring drops hourly while awake and every 2 hours during sleep for up to 2 weeks. Many patients could not fulfill these rigid requirements. Often after the first 7–10 days of this therapeutic regimen, ocular injection and conjunctival swelling occurred. In some patients, conjunctival edema caused blockage of lacrimal drainage, resulting in excessive tearing, which secondarily rendered the IDU applications ineffective. In addition, viral resistance to IDU drops occurred.

It was difficult to determine if failure of response to IDU was caused by viral resistance or improper application such as multiple skipped doses, with patients unable to consistently use drops hourly while awake and two-hourly while asleep, even after the introduction of IDU ointment for bedtime use. Because of these challenges with IDU therapy, alternate antimetabolite drugs were investigated.

Adenine arabinoside (ara-A) was the next antiviral medication to be investigated. Unlike IDU, ara-A was not incorporated into the DNA molecule. It displaced thymidine with iodine in that molecule. Ara-A was a nonspecific intracellular inhibitor of viral replication. It was available as an ointment, thereby requiring fewer applications. In multiple studies, ara-A ointment applied five times a day was as efficacious as IDU in treating dendritic superficial herpes simplex keratitis [9]. Patients using ara-A ointment had significantly less injection, burning and tearing, and the five times daily application was readily tolerated. It was also shown to be efficacious in cases of herpetic keratitis where IDU was less effective and/or intolerant [10].

Two different antiviral medications for treating herpetic keratitis were officially available for use in the United States by the 1970s, IDU and ara-A ointment. Neither of these was the ideal antiviral for treating this disease. Such an antiviral should be nontoxic and neither was. Ideally, a topical antiviral against herpes simplex keratitis should eliminate the viral growth in the corneal epithelium within the first two virus cycles or 48 hours after treatment initiation. Neither of the two available antivirals reached that efficacy. Therefore, the search for an ideal antiviral proceeded.

Kaufman and Heidelberger in 1964 [11] described a new antiviral, trifluorthymidine (F3T). Numerous studies in the 1970s concluded that this antiviral was the best choice of the three drugs approved by the United States FDA to treat herpetic keratitis. It still took an average of a little over 5 days for an epithelial HSV lesion, usually a dendritic ulcer, to completely re-epithelialize using trifluridine. F3T drops were prescribed nine times a day while awake. As with ara-A and IDU, F3T seemed to have little effect on stromal or disciform keratitis, metaherpetic keratitis, or herpetic uveitis, all corneal diseases which may not be directly caused by replicating herpes simplex virus.

Many ophthalmologists, particularly those practicing before the era of antiviral herpetic drugs, felt that rapidly removing herpes virus in the corneal epithelium, either in the form of dendritic or geographic keratitis, allowed for rapid healthy corneal re-epitheliazation and reduced the incidence of stromal disease or deeper forms of herpetic keratitis. Before the use of antiviral therapy, therefore, Gunderson's epithelial debridement with strong iodine solution or just gentle mechanical debridement of the epithelial lesion hastened healing of epithelial herpes.

Even after the introduction of antiviral therapy for epithelial HSV, there were many ophthalmologists who preferred initial debridement which quickly rid the epithelium of replicating virus, followed by patching until reepithelialization. We had seen patients at Wills who after such treatment quickly developed recurrent dendritic or geographic keratitis. Therefore, a study was designed to treat patients with epithelial HSV with either trifluridine (F3T) drops or debridement, followed immediately by a similar course of trifluridine or debridement alone and patching [12].

It soon became apparent that this third arm of the study, debridement and patching, led to herpetic epithelial recurrences in 4 to 10 days in almost 2/3 of the patients. In this study, debridement combined with trifluridine offered no advantage over the antiviral treatment alone. Until the era of oral antivirals and the even newer topical antivirals such as gancyclovir ointment, topical trifluridine drops continued to be the treatment of choice for epithelial keratitis.

Every corneal fellow and research associate who had the opportunity over a 60-year period to work and study with Claes Dohlman and his associates at the Massachusetts Eye and Ear Infirmary and the Schepens Eye Research Institute understand profoundly the unique qualities of this experience. The thoughtful genesis of ideas for projects and the meticulous

attention to details along every step of the work were the hallmarks of his relationship with those of us lucky enough to be a part of the Corneal Unit. All of the facets of Claes's leadership in my fellowship prepared me for my future 50-year career at Wills Eye Hospital. I am forever grateful to him for his friendship, guidance, and support.

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