



The Days of the Cornea Subspecialty: In the Beginning

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Background

In the late 1950s and early 1960s, there were no ophthalmic subspecialties. While some ophthalmologists expressed fields of greater interest, they all saw a variety of patients. No specialized postgraduate programs or formal clinical fellowships existed. Ophthalmology was not considered a discrete discipline but in conjunction with otolaryngology as a comprehensive eye, ear, nose, and throat specialty. Indeed, the American Academy of Ophthalmology and Otolaryngology represented both specialties and would conduct joint meetings. Not until 1979 did there occur a split into two separate entities, the American Academy of Ophthalmology and the American Academy of Otolaryngology [1]. Subsequently, otolaryngology added the discipline of head and neck to its title. It was in this climate that I first came to know Claes Dohlman.

In view of our long association, I was invited by the American Academy of Ophthalmology to contribute a chapter for this text to be published in honor of my mentor, good friend, and longtime colleague Claes Dohlman. The information presented herein is based on a talk presented at the Cornea Conference held in Boston in 2017 to

honor the many accomplishments of Claes Dohlman during his 60-year career. It is of note that over the past quarter century, I have attended several events dedicated to Claes' retirement, yet he continues to devote his full time to research, teaching, and patient care. There is no real prospect of Claes' retirement. Claes Henrik Dohlman will always continue to devote all his efforts to the benefit of his patients and profession.

Claes Dohlman has had an enormous impact on the practice and science of ophthalmology, not limited to the creation of the cornea subspecialty. A warm and friendly demeanor is the hallmark of his relationship with all, from the beginning undergraduate student to the most accomplished scientific minds and academic leaders.

Training

Following in the steps of his father, a chairman of ear, nose, and throat at Lund University in Sweden, Claes obtained his MD at Lund as well. He later received a PhD in medical research also from Lund University. He had trained earlier with Jonas Friedenwald at Johns Hopkins prior to returning to Sweden for PhD studies. What was proved to be the harbinger of an illustrious career occurred when Charles Schepens, having recently formed a research institute affiliated with Massachusetts Eye and Ear Infirmary, invited Claes to become one of the small numbers of

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research scientists. Edwin Dunphy then the Chair of Ophthalmology at Harvard and director of ophthalmology at Massachusetts Eye and Ear Infirmary provided Claes with a clinical appointment [2].

As I review the general circumstances surrounding Claes' achievements, it is clear that the environment which existed in Boston at the time, and in particular at the "Eye and Ear", constituted one of the enabling factors in his success. The juxtaposition of great clinical and scientific minds created a fertile environment in which he could ply his knowledge and expertise. Could the creation of a cornea subspecialty have been possible had Claes been offered a position in another institution in another city? I suspect his intellect and perseverance would have prevailed, achieving similar results even under diverse circumstances.

Historical Prospective

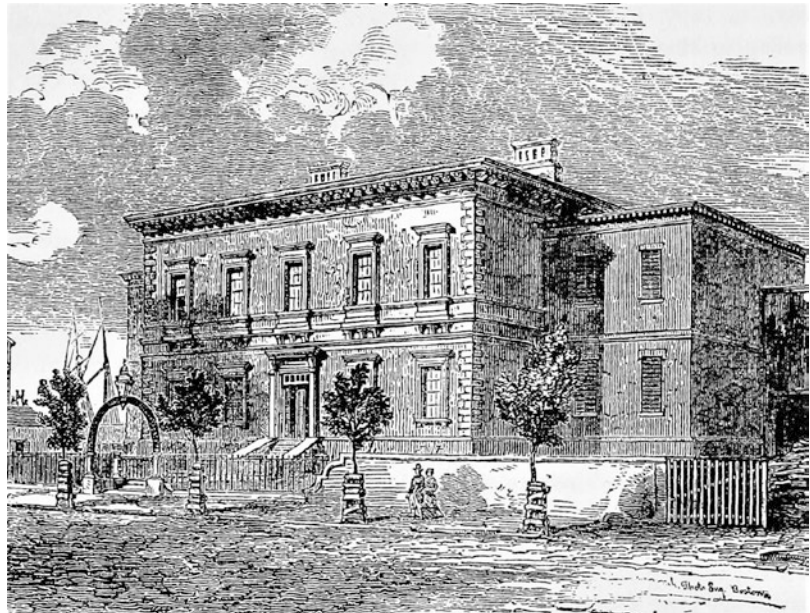
Massachusetts Eye and Ear Infirmary originated when doctors Edward Reynolds and John Jefferies established a charitable clinic (Fig. 2.1). Later in 1866, the first rotation of Harvard medical students occurred at the "Eye and Ear". This

subsequently evolved into a formal agreement for the teaching of Harvard students in ophthalmology and otolaryngology [3]. In 1932, Frederick Verhoeff was named to direct research and pathology at the institution, the Howe Laboratory having been formed in 1928.

Lucien Howe (1848–1928) received his medical degree from Harvard and practiced for 50 years in Buffalo, New York, prior to returning to Boston and establishing his laboratory. A number of Howe Medals are awarded annually, the most prestigious being that of the American Ophthalmological Society. Frederick Hermann Verhoeff (1874–1968) graduated from Yale in 1895 and received his MD from Johns Hopkins University in 1899. Verhoeff's impact was very significant. He was an individual with a management style perceived as being more dictatorial than collegiate. Over many years, he remained an active participant in patient care and research. I recall his presence at the weekly pathology conferences where he continued to forcefully express his opinions much to the chagrin of any junior physician presenting a case or defending a concept.

He frequently espoused his abhorrence of "the concealment of ignorance by the ostentation of seeming wisdom" [4]. His surgical techniques for

Fig. 2.1 A lithograph depicting the original Charitable Eye and Ear Infirmary. (https://commons.wikimedia.org/wiki/File:Massachusetts_Charitable_Eye_and_Ear_Infirmary,_Boston.jpg)



cataract surgery became so entrenched at his institution that the adoption of newer and more suitable techniques for cataract surgery were actually impeded. When asked if he was the best ophthalmologist in the country during a court proceeding his response was “there is no evidence to the contrary”.

While the mores of ophthalmic practice were relatively rigid everywhere at the time, Boston was fortunate to have been the venue for some of the great achievers in ophthalmology. In this crucible of great minds, Claes was able to interact with a number of other super achievers: Frederick Verhoeff, David Cogan, Charles Schepens, Morton Grant, Paul Chandler, Edwin Dunphy, and David Donaldson were among the many outstanding ophthalmic clinicians of the time.

Charles Schepens (1912–2006) lived in Belgium where he received his MD degree in 1935 from the University of Ghent. During the Second World War, he was an active participant in organized resistance to Nazi occupation. He escaped to England where he practiced at Moorfield’s Hospital, ultimately immigrating to the United States in 1947. He was a member of the Howe Laboratory, established the Retina Foundation and became a full professor of ophthalmology at Harvard in 1983 [5]. His Foundation soon became the source of numerous research and clinical developments, ultimately becoming an integral component of the Massachusetts Eye and Ear Infirmary’s research activities.

Edwin Dunphy (1896–1984) graduated from Princeton in 1918 and received his MD from Harvard in 1928. During the Second World War, he participated as a member of a special unit exploring the effects of poisonous warfare gases. He served as the Chairman of Harvard Ophthalmology from 1958 through the early 1960s [6]. He allocated the use of a small office in the rear of the main clinic floor as the first physical presence of what was to become the cornea service.

David Glendenning Cogan (1908–1993) was a 1929 Dartmouth graduate who received his MD from Harvard in 1932. His mother was an ophthalmologist as well. He became a member

of the Howe Laboratory, later serving as the Chairman of Harvard Ophthalmology (1955–1973) and Director of the Howe Laboratory from 1940 to 1974. He preceded Claes as the Chairman of Ophthalmology [7]. One of his early discoveries was the relationship of non-syphilitic interstitial keratitis with vestibular–auditory disease.

W. Morton Grant (1915–2001) established the glaucoma service at Massachusetts Eye and Ear infirmary and was an active researcher at the Howe Laboratory. He had graduated from Harvard and proceeded to acquire an MD from Harvard as well. He conducted research in ophthalmology and glaucoma without the benefit of formal residency training. His textbook “Toxicology of the Eye” was the first comprehensive study in the field [8]. Active collaboration with Paul Chandler later resulted in the creation of the Glaucoma Service.

Paul Chandler (1896–1987) received an MD from Harvard in 1924, and completed a residency at Mass Eye and Ear. While his individual accomplishments were numerous, the collaboration with resulted in the establishment of the Glaucoma Service in 1940. His textbook on glaucoma was authored with the assistance of Dr. Grant [9].

David Donaldson (?–1994) graduated from the University of Michigan in 1941 and was awarded an MD in 1945. He trained at the Henry Ford Hospital in Detroit where he worked with Henry Ford. Following residency in 1953, he became a member of the Howe Laboratory. His work with three-dimensional imaging photography of the eye resulted in the publication of two textbooks replete with slit lamp stereo photographs of anterior segment pathology [10].

The juxtaposition of individuals possessing strong accomplishments as well as strong egos created a scientific environment charged with political sentiment and noted for its lack of tranquility. While some institutions are organized in a group practice model, others have evolved into clusters of individual fiefdoms where there is a relative lack of allegiance to a common cause. Yet, Claes was able to survive multiple challenges during his tenure as Chairman.

Residents at the time included Richard Simmons, Herbert Kaufman, and Perry Rosenthal. And while the Schepens Foundation was in its infancy, the Howe Laboratory was in full operation so that a tradition of research was firmly in place at Massachusetts Eye and Ear Infirmary.

Initial Involvement

Following the completion of my residency in New York, I had the opportunity to participate in a few cornea surgery procedures performed by Ramon Castroviejo (1904–1987) and Benedict Rizzuti. Dr. Rizzuti worked at the Brooklyn Eye and Ear Hospital and Dr. Castroviejo at Columbia University as well as his private hospital. At the time, all ophthalmic surgery was performed with the surgeon standing. There were no stools or microscopes. My first introduction to an operating microscope was an awkward vertical Zeiss model originally designed as a laboratory device. Dr. Rizzuti had attempted to utilize a microscope for cornea surgery. Dr. Castroviejo had operating facilities in his 91st street home, a precursor to the ambulatory surgical centers of today. He wore magnifying loupes as did most eye surgeons at the time, and he too operated while standing. Some of his surgical procedures were filmed with commercial 35 mm film. He is credited for having performed the first successful cornea transplant at Columbia Presbyterian Hospital. He invented the technique of cutting the donor cornea transplant as a square rather than a circular piece of tissue. The main advantage of the technique was to enable the anchoring of the four corners in the peripheral recipient bed, thus limiting the formation of subsequent anterior chamber adhesions to the four corners of the graft (Fig. 2.2). Adhesions were common at the time, predisposing to angle complications and glaucoma [11].

I attempted to find an organized postgraduate teaching program in the field of cornea, but none existed. Edwin Dunphy suggested I travel to Boston and meet their new recruit, Claes Dohlman, who was interested in cornea disease.



Fig. 2.2 Photograph of Ramon Castroviejo circa 1930. (https://commons.wikimedia.org/wiki/File:Ramon_Castroviejo.jpg)

He had been joined by two local ophthalmologists also interested in the cornea, Arthur Boruchoff (1925–2013) and Edward Sweebe [12]. “Art” Boruchoff had graduated from Harvard in 1945 and received his MD from Boston University in 1951.

When I arrived in 1960, Dr. Sweebe had succumbed to a tragic illness, and his widow, Bobby Sweebe, became the receptionist/secretary for the unit. I was invited to participate in both the Foundation and the Clinic, and a modest amount of funding was procured. Claes has often described our initial meeting by my asking if I could be his fellow, and his now storied response was “what is a fellow?”

I was assigned to a small room on the top floor of the Charles Street Jail [13], notorious for having housed Sacco and Vanzetti, convicted terrorists, and later a former Boston mayor James



Fig. 2.3 Photograph of the Charles Street Jail as it appeared following its construction in 1851. (<https://www.flickr.com/photos/cityofbostonarchives/9321963420>)

Curley. The building was soon declared unfit for prisoners but obviously still considered suitable for fellows. The Charles Street Jail was first constructed in 1851 and subsequently purchased by Massachusetts General Hospital in 1991. The site was leased to developers who built the Liberty Hotel [14] (Fig. 2.3). The resulting structure maintained some of the original appellations such as the prison “yard” and “solitary confinement” rather than the traditional do not disturb notices appended to the room door.

And so I began to learn under Claes’ mentorship. In the clinic, I was exposed to the use of the newly developed topical steroids as well as the experimental use of idoxuridine for herpes simplex keratitis. Eeva-Liisa Martola and Stuart Brown made an appearance as unofficial and occasional members of the group.

In the Foundation, I was fortunate to meet the Director Andre Balazs and to work with Saiichi Mishima, Paul Payrau, Arvid Anseth, and Bengt Hedbys. David Maurice was a not infrequent visitor to our research facility. It is interesting to note that while these individuals pursued their

own independent projects, they were all involved in various aspects of cornea hydration.

Endre Alexander Balazs (1920–2015) devoted his productive life to the study of the structure and function of ocular connective tissues. He was asked by Charles Schepens to become the director of his newly established Retina Foundation and subsequently became an active member of the Howe Laboratory, while directing the work of the Foundation [15].

Jonas Friedenwald (1897–1955) was a 1916 graduate of Johns Hopkins University who received his MD also from Hopkins in 1920 [16]. He was an associate professor of ophthalmology when the young Claes Dohlman visited Hopkins participating in the work of his laboratory prior to returning to Sweden obtaining a PhD from Lund University.

David Maurice (1922–2002) trained with Sir Stuart Duke Elder at University College in London, receiving his PhD in 1951 [17]. He is well-known for his text on ocular physiology and having developed the principles of specular microscopy and confocal microscopy. He had

immigrated to the United States in 1968 and was on the faculty at Stanford University, later transferring to Columbia in 1993.

Saiichi Mishima (1927–2005) received his MD from Tokyo University and later studied with David Maurice in London [18]. He spent 2 years as a collaborator in Claes' laboratory at the Retina Foundation working with Arvid Anseth and Bengt Hedbys. His major work was in the area of fluid regulation in the cornea. He subsequently became the Chairman of Ophthalmology at the University of Tokyo.

Bengt O. Hedbys' working at the Retina Foundation was in the areas of cornea hydration, fluid flow, and cornea thickness changes. He collaborated with doctors Mishima, Arvid, and Payrau while in Claes' laboratory. He was a graduate of the University of Gothenburg [19, 20].

Arvid Anseth was born in Norway and obtained his MD from the University of Lund in 1961 prior to his tour at the Retina Foundation. His work at the Retina Foundation was based on the activity of cornea polysaccharides [21–24].

Paul Payrau also had a distinguished career as a member of Nazi resistance in France [25]. He along with his colleague Yves Pouliquen became a force in cornea research in France. He too is noted for his interest in cornea hydration, having proposed the transplantation of shark cornea tissue to ease the edema associated with Fuchs Dystrophy. He later became a member of the Rothschild Foundation research team.

When I arrived in Boston, the Schepens Retina Foundation was located in a converted west end tenement building with animal cages housed in the basement near the furnace unit. My technician was a Cuban expatriate, Antonio Gasset [26]. Claes later assisted Tony in gaining acceptance to medical school and he subsequently went on to become an ophthalmologist, working with Herbert Kaufman's department in Gainesville.

The Work Continues

From these meager beginnings, Claes brought forth and organized an entire cornea subspecialty. His dedication to both research and clinical

aspects was remarkable. He was a true patient advocate always searching for the truth, striving forward, and never allowing personal bias to intervene with research findings. His program involved uncovering and understanding basic biological and physiological principles, preliminary to developing appropriate and targeted medical and surgical therapeutic modalities.

This search for unvarnished truth, untainted by the prejudice of past or current ideas, is reminiscent of the tradition first espoused by Socrates with his admonition that we must not rely too heavily on the past. Words later recited by Plato in his dialogues of 360 B.C. and subsequently translated into Latin by Rodger Bacon as a part of his *Opus Magnus* in 1265 A.D.: "Sed Magis Est Amicus Verus". The greatest friend is truth [27, 28].

In those early days, clear corneal transplants were the exception. I recall Claes showing me a clear graft in an eye subsequently blinded by glaucoma as the result of unrestricted use of the newly developed topical steroids. This concept of induced glaucoma he has carried on is evidenced by his insistence on the use of shunts in combination with keratoprosthesis devices.

Keratoprosthesis

The Columbia Presbyterian team of Arthur Devoe [29], Ramon Castroviejo (1904–1987), and Hernando Cardona [30, 31] implanted a number of early Cardona model devices in the late 1950s and early 1960s with generally unfavorable results. The device was individually manufactured in Columbia and shipped to the United States. It was available only in one aphakic power, but there were three models. The simplest had an iris design and either blue or brown coloration to its surface with the optical cylinder passing through a 3 mm opening in the subject's diseased cornea, secured by a threaded small posterior plate. It was termed the "Nut and Bolt" design (Fig. 2.4). The most common model involved a polymethyl methacrylate plate which was sutured to the cornea surface (Fig. 2.5). A central threaded 3 mm opening allowed the

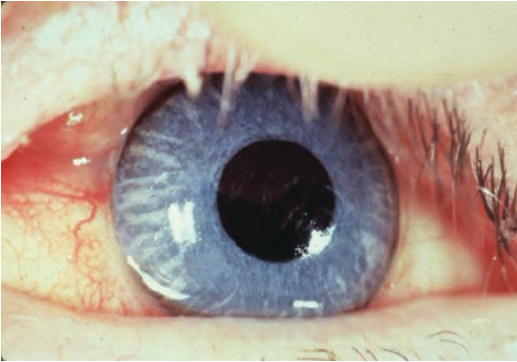


Fig. 2.4 The Cordona Nut and Bolt keratoprosthesis. Note the blue colored pattern of the front plate designated to match the fellow eye

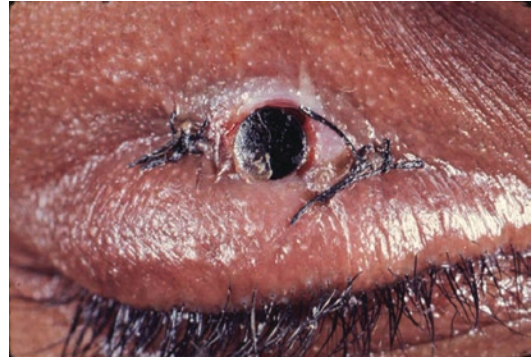


Fig. 2.6 The Cardona Through and Through model keratoprosthesis following surgery. Note the protrusion of the optical cylinder through the upper lid

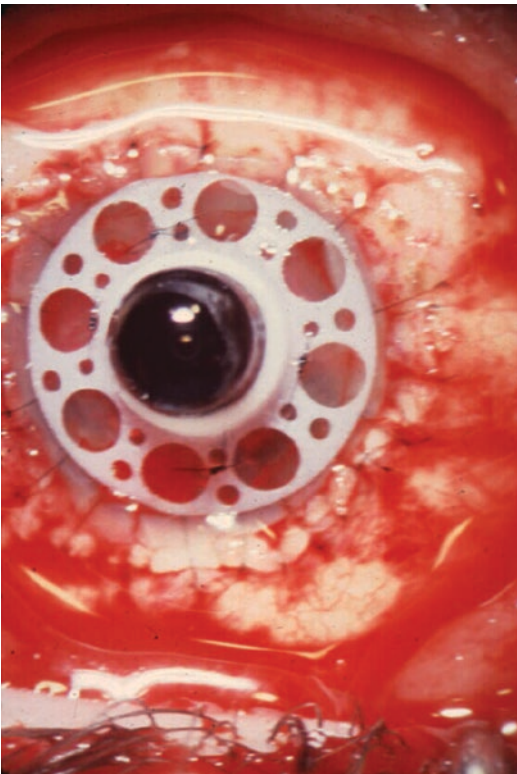


Fig. 2.5 The standard model Cardona keratoprosthesis in place covering the anterior cornea surface prior to placement of sutures

optical cylinder to pass through the cornea and protrude into the anterior chamber. It was often covered by buccal mucous membrane or perios-teum. The third variety was termed the “Through and Through” and was designed to pass through

the tarsus of the upper lid prior to a permanent tarsorrhaphy (Fig. 2.6). I had participated in a few of these procedures and noted that 100% were ultimate failures. Yet, over his 60-year career of dedicated KPRO research, Claes ultimately devised the Boston I device and success followed. The unit was first known as the Doane-Dohlman device. Claes had insisted on giving full credit to his collaborator.

Claes had become intrigued by the early work of Edward Stone [32], working in the Howe Laboratory to implant plastic materials in rabbit eyes, and then evaluating the Cardona device [30]. Thus began the Dohlman interest in bio-compatibility issues which must support device implantation. These early subjects all had end-stage disease, albeit originating from a variety and combination of disease entities.

The number of these complex cases was small, and many months of observation were necessary prior to attempting modifications in either surgical procedure or device construction which then again must be evaluated over time. The Food and Drug Administration was becoming interested in medical devices and new regulations were proposed. The Doane-Dohlman device was ultimately approved for human use in 1991. Numerous modifications followed prior to the introduction of what we now call the “Boston I” device. Others involved in keratoprosthesis work at the time were mostly interested only in the clinical applications rather than in basic research aspects. Aside from the original Columbia

University team in the United States, Louis Gerard in Texas, Peter Choice in England, the Barraquers in Columbia and Spain, the Russian Group in Odessa, and the Italians represented by Strampelli, Franceschetti, and Falcinelli were all active at the time. Unfortunately, there was no coordination, and the number and variations of devices and techniques proliferated with little overall improvement in results over time.

While formerly active in the field, I had become discouraged with the results, and had not implanted any devices for almost a decade. With the dawn of the twenty-first century, Claes [33] related to me the details of his new design and the concept of covering the implanted device with a bandage contact lens. Other innovations included the fenestrated back plate, the insistence on the use of prophylactic antibiotics, and the anticipation of elevated intraocular pressure. After only a few cases, I became a strong advocate and ultimately modified the surgical techniques to enable primary implantation in newborn infants [34]. A process encouraged by Claes while disparaged by a few other members of his Boston group. The use of the Boston type I device has proliferated worldwide. An early impediment was cost. But arrangements for manufacture in other sites, combined with some device manufacturing changes, now have the prospect of significantly increasing the availability of this technology even in impoverished countries.

Claes Dohlman's entire efforts were always focused upon delivering help to over 2 million individuals with irreversible cornea blindness not amenable to corneal transplantation and mostly located in third world countries. The resultant Boston I device has been implanted in over 15,000 eyes worldwide as of this writing.

The Research Continues

Clearly much work remains. There are complications to be addressed and avoided, as well as new techniques to be evaluated. The current keratoprosthesis laboratory at Massachusetts Eye and Ear Infirmary has been modeled into a research unit engaged in studying new materials, device modifications, related elevation of pressure and

intraocular inflammation, as well as many aspects of cost and distribution. From its inception, all of the funds generated were devoted to the laboratory and teaching. Claes has never received any remuneration from the sale of the device he invented.

While I may have been the first to be exposed to Claes' level of dedication, his impact on me was insignificant compared to impacting all of ophthalmology merging cornea research, education, and therapeutics into an integrated cornea subspecialty. Several hundred cornea fellows, post-doctorate PhDs, and colleagues throughout the world have been trained and become disciples. They in turn have established and led cornea programs in their own countries and institutions. His leadership does not allow for complacency. Claes Dohlman has taught us all to continually strive for the next level, to grasp Socrates' *Magnus Verus*.

From the fundamental work uncovering physiological concepts and the workings of cornea swelling pressure, stromal thickness changes, and the flow of aqueous into and out of the stroma under the control of the endothelial pump to Paul Payrau's attempt to implant elasmobranch cornea tissue to control Fuchs dystrophy, and now the Boston I device, his dedication to truth proliferates. We now have the proposed use of TNF alpha inhibitors not only in keratoprosthesis surgery but to mitigate pigment epithelial apothecosis and optic nerve damage following severe ocular injury [35].

In the final analysis, consolidation of a cornea subspecialty is truly a unique accomplishment. For over 60 years, generations of scientists and clinicians have gone forth to propagate Claes' concepts and techniques, now culminating in a means to correct otherwise irreversible cornea blindness.

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