If anyone deserves to be honored as the most influential American ophthalmologist of the 20th century, Frederick H. Verhoeff, MD (1874-1968) certainly does. This man enjoyed a very long career as a professor of ophthalmic research at Harvard University (Cambridge, Mass) and the chief of ophthalmic research at the Massachusetts Eye and Ear Infirmary (Boston).\textsuperscript{1-8} He made important contributions to a wide range of ophthalmic topics, from pathology and physiology to surgical techniques. The American ophthalmic pathology society is named in his honor, for it was largely his work that established the subspecialty of ophthalmic pathology. Independent, aggressive, and full of energy, he continually challenged his colleagues to be honest, even skeptical, observers if this would promote the scientific basis of patient care. He set very high standards for himself and expected the same of others. He published hundreds of journal articles over a 67-year period, the last at age 92 years on his perceptions of his own retinal venous occlusion.

Shortly after Verhoeff’s death in 1968, David Cogan, MD (1908-1993) delivered an emotionally charged eulogy on his behalf.\textsuperscript{9} Cogan succeeded Verhoeff as head of the Howe Laboratory at Harvard Medical School and served as chairman of the Department of Ophthalmology. His tribute took the form of a letter as though Verhoeff were still alive, perhaps retired and living in the countryside.

Dear Freddie, When I asked you what led you into ophthalmology, you gave me a direct and simple answer... Your father gave you a camera for your 12th birthday... That gift of a camera marked the first milestone in your career as an experimentalist.

Verhoeff had tested its limits and became fascinated with lenses. His interest in optics led to a determination to become an ophthalmologist. He graduated from the Sheffield Scientific School at Yale (New Haven, Conn) in 1895, and from the recently established Johns Hopkins Medical School (Baltimore, Md) 4 years later. Verhoeff was the first graduate to enter the field of ophthalmology. Cogan continued:

The new school promised to inject the quality of skepticism into medical education and to shake the complacency of the established medical schools in this country. I know this was to your liking. Even the agnosticism represented by having the elder Huxley give the inaugural dissertation at the opening of the University and by the scandalous omission of prayer from the ceremony must have given you a feeling of vicarious ecstasy.

Things fell into place for Verhoeff. As a medical student he showed such a strong interest in ophthalmology and research that the head of ophthalmology at Johns Hopkins arranged for him to present a paper to the American Ophthalmological Society before graduation. During his externship the year following medical school, the Massachusetts Charitable Eye and Ear Infirmary was looking for a pathologist. The dean at Johns Hopkins medical school, William Welch, was asked to nominate a candidate. He approached Verhoeff, who was doubtful since he had no special knowledge of ocular pathology. With Welch’s encouragement he took the job at a salary of $650 per year (no assistant, technician, or secretary was provided).
You were becoming established, and even the Boston conservatives, who had had no difficulty in restraining their enthusiasm for an upstart from Johns Hopkins, were beginning to realize you were someone to respect. I am sure that your early encounters with the Boston Establishment did not ameliorate your native abhorrence of ostentation and false authority.

After spending 2 years at the Infirmary, Verhoeff went abroad for 8 months of further study. He spent a wanderjahr with several of the great men in European ophthalmology: Ernst Fuchs (1851-1930) in Vienna, Otto Haab (1849-1931) in Zurich, and Sir J. Herbert Parsons (1868-1957) in London. Cogan continued, “You were to be their counterpart in America. Returning to Boston you followed their footsteps but always with a distinctly Verhoeff gait and with exploration of entirely new pathways.” A steady stream of publications and awards followed. This was recognized in Baltimore, where the great William Osler tried unsuccessfully to woo him back.

What was the method behind Verhoeff’s success? He was intensely interested in the whole field of ophthalmology, worked terribly hard, wrote and spoke clearly. Cogan wrote:

First of all, and possibly above all else, you were intellectually honest. You said what you thought, let the chips fall where they would. You had no patience with pretense or unsupported authority and you could be frightfully devastating at medical meetings. As Derrick Vail once remarked, many a timorous author rued the day he was on the program when you were in the audience. It made no difference who the essayist was because to you ideas took precedence over the man.

His candor was legendary. One presenter was told he “must have overlooked my latest paper on the subject. I have an idea that if he had seen the method there described, he would not have worked out this one.” He advised another man he “would find it instructive and interesting to pursue further a study of the literature.” Verhoeff could be hard on himself. When no one volunteered to discuss one of his manuscripts, he began by tearing apart the paper, then acknowledged that it had some good qualities under the circumstances. Another time he admitted “I have discussed this matter without knowing a damned thing about it.”

Cogan concluded “You have left us now, Freddie, and a new generation will be coming along that knows you only by name. They will have missed a lot. Your going is the end of a very personal experience for those who came under your influence.” Cogan felt the passing of the Verhoeff era might mark “the end of a period in which persons like you could develop the independent and unorthodox approach to life and ophthalmology that enlivened the field in America.

How might Verhoeff have replied to this tribute?

Dear Dave,

I have missed everyone in ophthalmology tremendously since you wrote me some 30 years ago. However, I have not been inactive. I have been watching the development of the field from afar and would like to describe what I have seen. Perhaps the best approach is to update my article “American Ophthalmology During the Past Century,” 10 which was published more than 50 years ago. Initially, I found the vastness of the subject daunting, but the passage of time has allowed me to clarify my views.

A logical place to begin is at the middle of the 19th century, when there were no true ophthalmologists in this country. Physicians were generalists. Although a few physicians spent a large amount of their energy on diseases of the eye, this may have been in response to demands placed on them, rather than an active decision to restrict their practices. Any of several men could be considered the father of American ophthalmology (eg, Elisha North of New London, Conn, Philip Syng Physick of Philadelphia, or George Frick of Baltimore), but no records tell us who the mother was. The few American ophthalmologic textbooks of that time depended heavily on European models. Although these books are only of historic interest today, they follow anatomic classifications of disease in general and most of the terminology is still in use. Notably missing are descriptions of disease of the posterior pole of the eye, since Hermann von Helmholtz did not publish a description of his landmark invention, the ophthalmoscope, until 1851. No physician owned a set of trial lenses, and refraction was not performed. Glasses could be obtained from opticians, but there was no correction available for astigmatism. Local anesthesia was not available (Karl Koller did not discover the anesthetic effect of cocaine until 1884) but general anesthesia using ether was possible. The primary surgical procedures were cataract extraction or discission, enucleation, and creation of an artificial pupil. Glaucoma was occasionally treated by paracentesis, but the iridectomy and filtration procedures had not yet evolved.

Ocular therapeutics has changed drastically since 1850. Atropine was available, but the use of pilocarpine to lower intraocular pressure was not discovered until 1877. Topical agents in common use included mercury bichloride, silver nitrate, zinc sulfate, zinc oxide, copper sulfate, lead subacetate, tincture of iodine, sodium borate, camphor, and opium. Oral agents included strychnine, quinine, turpentine, and iron. Bloodletting, purgatives, setons, blistering agents, and leeches were also employed.

Specialization was anathema to the medical profession, since it implied that some physicians were more qualified than others. Even when the American Ophthalmological Society was founded in 1864, many of its members, including its president, practiced general medicine and surgery in addition to ophthalmology. Separate ophthalmic hospitals were founded in several major eastern cities during the first half of the 19th century because general hospitals lacked appropriate facilities for the specialty. This separation soon proved to cause problems, so most facilities of this type established close ties to other hospitals or medical schools.

The field evolved much more rapidly during the second half of the 19th century. I have always been interested in “firsts.” The first chair in ophthalmology was created in 1860 at the Miami Medical College, now the University of Cincinnati, for Elkanah Williams (1822-1888), an important educator and author who is...
programs that have evolved during surgery (I introduced conjunctival-scleral suturing in 1916).11,12)

... from a cult which formed an anemic reflection of European ideas adopted at second hand, and often late, to a discipline which has assumed a position of leadership unchallenged throughout the entire world both in the excellence of its practice and the importance and mass of its contributions to new knowledge.16

The following are the highlights of what I have observed in the practice of ophthalmology during the last 100 years.

CATARACT

During the early years of the 20th century we all came under the influence of Henry Smith, the fascinating Englishman who perfected intracapsular surgery in India and kept a cigar in his mouth whenever he operated. The intracapsular method was used for adults and extracapsular surgery (linear extraction) for children. Cataract surgery posed a far greater challenge then than now. A young adult with a dense cataract, tightly adherent to the vitreous, was a difficult problem. Extracapsular surgery was nearly always followed by opacification of the posterior capsule, which meant a second operation would be needed. Early in my career the anesthetic agent available was topical cocaine. Later, subconjunctival injections were employed. I used a fornix-based conjunctival flap and placed 1 to 3 silk sutures. So far as I can tell, I was the first to use a nonperforating appositional suture, the first to use more than 1, and the first to include conjunctiva in the suture.17

I made a corneal incision superiorly with a von Graefe knife. At
first I operated through a dilated pupil and made an iridectomy for better exposure and to prevent glaucoma. Most surgeons removed the lens with capsule forceps, grasping it inferiorly and tumbly it out. I devised a better method. I found it easier and safer to slide the lens out by grasping it superiorly. Preoperatively, I instilled pilocarpine to constrict the pupil and keep the vitreous back. I made a radial iridotomy above for visualization.

The complications encountered today occurred in those days, but more often. With no posterior capsule or intraocular lens to hold the vitreous behind the pupil, it would occasionally touch the cornea and opacify it (I may have been the first to describe this). In one case, I operated on the first eye, doing an intracapsular extraction without any vitreous loss. Everything went well and the resultant visual acuity was 20/20. However, during surgery on the second eye the pupil remained round, but vitreous adhered to the upper half of the cornea, causing considerable edema. I attributed the vitreous loss to the patient misbehaving during the surgery. Today we would do a vitrectomy, but then my approach was slightly different. I reoperated, letting out as much vitreous as possible, but not cutting it. The cornea cleared except for a tiny area well out of the visual axis, and the anterior chamber no longer contained vitreous. However, the pupil became updrawn (I enlarged the pupil later), and the visual acuity improved to 20/30. I reasoned that removal of a large amount of vitreous would be better than just a little, for after a large loss the remaining vitreous is more likely to remain behind the pupil. If the posterior capsule ruptured during surgery and the lens fell into the vitreous, I found it possible to bring it forward with careful irrigation.

Despite not having operating microscopes or current techniques of wound closure, we encountered choroidal detachments infrequently. These were sometimes treated by draining fluid through a scleral puncture. I found it even more remarkable that epithelial down-growth into the anterior chamber rarely follows cataract surgery. Our wound closures rarely ruptured, except after severe trauma such as a fist in the eye. Even though we had no corticosteroids, we rarely encountered much inflammation after intracapsular cataract surgery. On the other hand, extracapsular extraction left more lens material behind and resulted in more iridocyclitis. Microscopic examination of eyes that had undergone intracapsular surgery revealed little inflammation.

We encountered retinal detachment infrequently after cataract surgery and debated whether this was more likely to occur without an intact capsule. Theoretically, an intact capsule should offer more support for the vitreous and decrease retinal traction. However, removal of the rest of the lens does allow the vitreous to come further forward than in the unoperated eye. We did not have an adequate number of cases to answer the question statistically.

**REFRACTIVE SURGERY**

The most grateful patients I ever had were those with severe myopia who underwent lens extraction. I did extracapsular procedures for several young individuals whose lenses were clear and each resulted in markedly improved vision. I was always concerned about the possibility of retinal complications, but did not notice an increase in detachments in this population. There was less vitreous loss than is usually reported; of course, phacoemulsification and the YAG laser had not been invented by that time. I found that recovery to normal vision took longer than usual in these cases, and presumed this was due to macular edema.

**CORNEA AND EXTERNAL DISEASE**

Sometimes the most unusual cases lead to interesting findings. I worked in Boston, which is nicknamed the land of the bean and the cod. One day a young fisherman who had gotten codfish bile in 1 eye came to see me. The injury resulted in a corneal opacity. The Bible tells us that Tobias cured his father’s blindness with fish bile. Jonas Friedenwald and I had performed rabbit experiments using fish and ox bile and found that bile can remove the corneal epithelium without damaging the stroma. (I often experimented on my own eyes, but felt it more prudent in this case to use an animal model.) Our patient had used lead acetate drops to treat his problem to our grave disappointment, for we had also found that lead acetate can cause permanent corneal opacities and recommended elimination of lead from all over-the-counter eye-drops. Since bile has antibacterial and solvent properties, other investigators tested it in the treatment of corneal ulcers prior to the advent of antibiotics but the bile did not penetrate deeply enough to be effective. We tested the therapeutic value of bile in treating herpes simplex keratitis. Unfortunately, it worsened the disease.

Herpes simplex keratitis occurred fairly commonly during treatment of lues. I saw many cases associated with treatment using arsenicals. Others reported an association with malarial treatment of neurosyphilis. Undoubtedly, the stress of these forms of therapy caused endogenous release of many chemical mediators, including corticosteroids, which activated the virus. Fortunately antibiotics and antiviral agents have since been developed, but we are all concerned about microbial resistance.

We have long known that the herpes simplex virus is stored in the Gasserian ganglion, and that it can travel down the corneal nerves to cause recurrent attacks of inflammation in the central cornea. Herpetic involvement of the peripheral cornea may be due to the virus following conjunctival nerves. From this I reasoned that the peripheral keratitis of rosacea followed a nerve distribution, and doing a partial conjunctival periectomy at the limbus would heal the cornea. My results were good, but I do not seem to have convinced anyone else. Perhaps some future investigator will take up my method, or I will have to include this technique in a revision of my article titled “My Major Mistakes.”

I recall distinctly the first reports of penicillin’s effect on bacte
ria. Baron Howard Florey, who received the Nobel Prize for his work with this landmark in antibiotic therapy, described its usefulness in treating ocular infections in his first clinical report. Penicillin penetrates the cornea rather poorly. Ophthalmologists soon began to inject penicillin into the anterior chamber and the vitreous to achieve a high concentration at the site of infection. Recalling the retinal toxicity of other agents injected into the vitreous, I raised questions about this method. Toxicity of antibiotics remains an important concern.

Several decades before the inception of penicillin and sulfonamide therapy I published an article on the treatment of hypopyon keratitis. The ideal agent would destroy the microorganisms without causing serious tissue injury. I experimented with a large number of antiseptics and found their germicidal activity was inactivated by serum in every case. Argyrol, an organic silver salt, was ineffective, a fact that has recently been rediscovered. Keratectomy and conjunctival flaps did not work. Zinc sulfate and analine dyes such as methylene blue were not helpful either, and while cautery with heat or chemicals and ultraviolet light will kill bacteria, effective treatment levels cause considerable tissue damage. The only topical therapy I found effective for corneal ulcers was iodide solution.

I published the first description of the pathology of superficial punctate keratitides. The opacities are due to necrosis of a leukocytic infiltrate immediately beneath the Bowman membrane. The corneal lamellae were simply split apart, not destroyed, which explains why the lesions can disappear without leaving a trace.

Corneal transplantation has become so successful that we tend to forget its development during the second half of the 20th century. Before this technique became popular, we would often perform a superficial keratectomy to remove corneal opacities. I found corneal transplantation particularly useful in lattice corneal dystrophy. Because the cornea is often very thick in this entity, the dissection can be done rather easily. Our understanding of other corneal dystrophies has improved markedly. The pathology of Fuchs dystrophy interested me. The corneal endothelium seems to be a simple tissue that should be able to heal itself after injury, but it is very unique. I do not know of any other simple layer that will produce a tissue like the Descemet membrane beneath it.

We encountered severe allergic reactions to medications relatively frequently. I recall one patient who knew she was sensitive to atropine but did not tell us about it and lost an eye from only 1 or 2 drops. Her face looked as though she had erysipelas and she developed a keratitis that became a total corneal ulcer. To prove this was the result of the atropine I asked an intern to test her. He injected a small amount of atropine into the skin. There was no reaction after 24 hours, so he retested with a larger dose. Within 24 hours there was a massive amount of inflammation. A patient who was allergic to pontocaine developed a severe reaction when I forgot she was allergic and instilled the substance. I told her that if she got the reaction 1 more time it was her fault, because she should have reminded me not to use that anesthetic.

Dry eye syndromes can now be treated rather effectively with lubricant drops and punctal plugs. I used to employ a rather simple method to block the lacrimal drainage system. I would place a pin in the canaliculus and dissect around it, closing the area with sutures. To see if the procedure will be helpful, you may place a suture temporarily around the canaliculus.

Sir Stewart Duke-Elder named me the “Grand Old Man of American Ophthalmology” and dedicated a chapter of his System of Ophthalmology to me. He wrote that I was “the first investigator to elucidate the pathological basis of the ocular manifestations of collagen disease.” He was referring to my report on scleromalacia perforans, which linked it to rheumatoid arthritis.

GLAUCOMA

Modern concepts of the source and rate of flow of aqueous and the regulation of intraocular pressure were beginning to be understood when I described the association in 1925. Therapy has changed markedly since that time. Trabeculectomy, antimetabolites, lasers, and most of the pharmacological agents in use today were not available during my years in practice. Various forms of filtration surgery have been available for a very long time, however. Trephine procedures beneath a conjunctival flap were pioneered by Freeland Ferguson and Robert Elliot in 1909. The following year I published my method of making an opening in the sclera. I named this procedure a sclerostomy, and the terminology has stood the test of time. Since a major complication of this procedure is injury to the lens, I provided a guard for the trephine. Later I described another modification, a motorized trephine to improve on the manual variety.

Creating an opening in the sclera is not the only important aspect of filtration surgery. At least as important is maintaining adequate drainage of aqueous through the opening. Paul Chandler and I described a new method of doing this through an incision high in the superior conjunctiva.

I examined microscopically many eyes in which filtration surgery failed to control the glaucoma. Some of the most difficult cases were those of hemorrhagic glaucoma, in which tissue proliferates and closes the entry. I reported the first pathologic study of a successful sclerostomy opening in 1921. The opening was filled with delicate connective tissue.

In 1924 I described a cycloectomy operation that might be effective in many forms of glaucoma. A small piece of the pars plana is excised. The incision through the conjunctiva is sutured closed, but the scleral entry is not. In cases of glaucoma that failed to respond to standard filtration procedures, we sometimes attempted to shut down aqueous production by the ciliary body. We were limited to either a cycloectomy or cyclodiathermy. Newer procedures have higher success rates and fewer complications.

UVEITIS

Scientific evaluation of sympathetic uveitis began with William Macken-
zie's work in 1835. Fifteen years later, prompt removal of the injured eye was advised to protect the other eye. For at least a century investigators have tried to link an infectious organism to this disease. While the germ theory makes some sense, I pointed to evidence that allergic phenomena may be involved.54 Later I realized I had a century. I considered it a relatively skeptical of this type of theorizing.53 ...tions by direct evidence, I was skeptical of this type of theorizing.53 I was advised to protect the other eye. For at least a century investigators have tried to link an infectious organism to this disease. While the germ theory makes some sense, I pointed to evidence that allergic phenomena may be involved.54 Later I realized I had...
bright plaques in the retinal arterioles. In my comments on his presentation in 1961, I was forced to admit, "I really don’t know a thing about the subject, but I can’t resist the temptation to discuss it from a theoretical standpoint." What made the most sense to me was that these plaques were embolic, not thrombotic, in origin. To explain the vascular occlusion, some crystals may not completely block a vessel, but can cause others to accumulate and finally cause a large obstruction.

I witnessed tremendous advances in the treatment of retinal detachment. I recall how dismal the results of surgery were early in my career. Jules Gonin (1870-1935) is credited with the innovative thinking that led to improved results.73 In 1918 he said that separation of the retina was always associated with a retinal hole. He emphasized the need to seal the hole. In 1920 he gave a preliminary report of his surgical technique, which included cauterizing the sclera in the region of the tear. In the 1930s Gonin’s disciples modified his technique, using diathermy. The scleral surface was treated to elicit an inflammatory response in the underlying choroid and create a scar that would hold the retina in place. Diathermy was also used in a puncture mode to wall off the retinal break. Perhaps I have not been given due credit for my method of treating retinal separation using electrolytic punctures, which was published in 1917.72 I believe this was the first report of using multiple scleral punctures to fasten down the retina.73 Later I injected fluid into the vitreous through the pars plana to help treat the detachment. It is interesting that many recent refinements in vitreoretinal surgery have started from similar principles.74

Retinal separation without hole formation is an interesting phenomenon. I reported a case many years ago.75 When this subject came up before, I was so deaf that I cannot hear the subject.”76 Experience has led me to conclude that separation of the choroid may cause separation of the retina, but the converse is never true.

Gerd Meyer-Schwickerath pioneered photocoagulation to treat retinal vascular disease in the mid 20th century and the use of lasers followed. Before these advances were available, diathermy was available but had the disadvantage of causing tissue destruction. As far as I know, I was the first to use diathermy to treat recurrent retinal hemorrhage and retinitis proliferans.55,77 I suggested that this treatment might be useful in bypassing retinal vascular obstruction from any cause and might help establish communication between the retinal and choroidal circulations. Other investigators have accomplished this feat recently using lasers.

What new developments will the 21st century bring? Forecasting the future has always been hazardous. At the beginning of the 20th century several eminent scientists were asked for their predictions.77 Some were close and some were ridiculously far off. One eminent British surgeon, Thomas Bryant, felt the acme of science had been reached, that medicine had gone about as far as it could. He suggested that the great 19th-century advances in anesthesia and antisepsis would not develop further. He was more optimistic in stating that recent progress in bacteriology “clearly foreshadow both the prevention and cure of diseases that are now generally regarded as hopeless,” including tuberculosis and cancer. The unexpected discovery of x-rays in 1895 showed him how difficult it is to make predictions. I cannot do any better than this, other than to state that I know we will be surprised.

Best wishes to all for the new millennium.

Fondly,
Freddie

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