Trachoma has been one of the most blinding diseases in the history of ophthalmology. From its initial description in antiquity until the late 1930s, no specific treatment or effective cure had been known, and the only expedient had been to destroy the diseased tissue containing the infectious agent, rendering the disease inactive. Virtually all medical, mechanical, and surgical treatments were unsatisfactory, with cure rates of approximately 20%. Therapy for trachoma had barely advanced from the measures used by the ancient Egyptian, Greek, and Roman physicians. All prior therapies became obsolete in 1938 when Fred Loe, MD, working on an American Indian reservation, introduced sulfanilamide as a treatment of trachoma, achieving a 90% cure rate. One of the most unusual aspects of Loe’s career was that he had no formal training in ophthalmology and was completely self-taught as an ophthalmologist.

In the history of ophthalmology, 2 diseases predominate for their long history, their wide-ranging effect on blindness, and their continuing importance in the contemporary world: cataract and blinding keratoconjunctivitis, known previously as ophthalmia. Among the subtypes of ophthalmia, by far the most prevalent and important is trachoma.

The World Health Organization estimates that in 42 developing countries, endemic trachoma currently affects approximately 40 million people, of whom 8 million have trichiasis and vision loss. Although it is second to cataract as the most common cause of blindness worldwide, it is the most common preventable cause of blindness.

On July 1, 1798, trachoma and other external-eye diseases became a medical problem of the first magnitude: on that day, the French revolutionary army, led by General Napoleon Bonaparte, invaded Egypt. Europeans who previously had visited Egypt had commented on the extraordinary prevalence of eye diseases in that country, and in 1745, one traveler described Egypt as the “land of the blind.” The French, British, and other armies that invaded Egypt experienced severe trachoma and other infectious subtypes of ophthalmia while in that country. When the soldiers who fought in Egypt returned to their native countries, these infections were carried back to Europe and were further disseminated by the masses of soldiers marching across the European continent in the Napoleonic wars from 1798 to 1815. From Europe, trachoma and secondary infections became worldwide pandemics. At that time, trachoma was known as the military or the Egyptian ophthalmia; only later was its present name applied. For decades, trachoma had a greater effect on civilian and military affairs than any other disease since the bubonic plague. In the past, this disease had spread throughout the world, but during the past century, it has virtually disappeared from developed countries. Today, trachoma is found only in areas in which poverty, lack of personal and communal hygiene, lack of water for washing, and inadequate health care are prevalent.

What discoveries and factors led to the eradication of trachoma in the developed world? The first was the marked increase
and miasma arising from decaying earth, water, and organic matter. Egyptian ophthalmia was attributed to various climatologic factors, such as the intense light of the sun, the blowing of dust in the wind, the dryness of the desert air, or, contrarily, the moisture of the Nile River. It is to the credit of British military physicians that they insisted and demonstrated that ophthalmia is contagious. The most important of those physicians was John Vetch who, in 1807, emphasized that the mechanism of contagion was exclusively the conveyance of pus from a diseased eye to a healthy one. Vetch’s insistence on more careful hygienic practices in military barracks, such as issuing a towel to each soldier, markedly reduced the spread of ophthalmia. Vetch did much to discredit the fiction that the disease could be propagated through the air, by merely looking at a diseased eye. Although the idea of contagion was resisted by many physicians, Vetch provided the first evidence in its favor and the first attempt to limit the spread of the disease. The third factor that markedly reduced the prevalence and severity of trachoma was a treatment that was effective and safe. Before the introduction of sulfanilamide therapy in 1938, no specific treatment was known, and the only expedient was to destroy the involved tissue harboring the infectious agent, rendering the disease inactive. No ocular disease was considered more stubborn and difficult to eradicate than trachoma. As one might expect for a disease so widespread and persistent, the types of therapies were legion.

The first line of therapy was medical. Physicians in the 1930s relied on essentially the same agent used by the ancient Egyptian, Greek, Roman, and all subsequent physicians: copper sulfate in crystalline form, known as the “blue stone.” This chemical, mounted in a wooden or metal handle, was used to scour the conjunctiva daily for many months or years until the disease became quiescent (Figure 1). Often, alum potassium was substituted or the 2 caustic metals were used alternately in therapy. Diseased eyes were often treated with drops of silver nitrate, zinc sulfate, or other antiseptic or astringent chemicals. Another medical technique was to massage the diseased conjunctiva with a glass rod or a cotton-tipped applicator moistened with caustic solutions or chaulmoogra oil, once used to treat leprosy. Eventually, most cases became inactive, although it may have taken months or years for this to occur, and relapses or reinfections were common. The process was painful, even after the introduction of cocaine for topical anesthesia. Medical therapy was virtually always prolonged because no means existed to eradicate the infectious agent of trachoma without causing further injury to the ocular surface.

The next line of attack was mechanical. Often, the diseased conjunctiva was simply curetted or scraped. This approach had been used since ancient times when stiff, sharp vegetable leaves were used to scour the conjunctiva. In the latter half of the 19th century, a new concept was developed to attack the active disease: the soft trachomatous follicles of the tarsal conjunctiva would be expressed and mechanically removed from the eyelids rather than trying to destroy the disease with the application of copper sulfate. Many different maneuvers were invented to express the follicles. Roller forceps were closed on the everted eyelids and firmly drawn over the eyelid to express the soft follicles; the remaining follicular material was then scooped out with forceps or curettes (Figure 2). The raw areas were then massaged with various antiseptic agents, such as copper sulfate, or treated with galvanic current, carbon dioxide ice, diathermy, or even radium or radiotherapy. Grattage was a painful procedure performed by vigorously rubbing the diseased conjunctiva with a steel toothbrush-like instrument dipped in corrosive chemicals, such as bichloride of mercury. A variation to using a mechanical instrument to scrape the conjunctiva was to abrade it with sandpaper.
lated tissue, cautery with hot needles, and various procedures to correct entropion and trichiasis. When the entire eyelid was grossly thickened and diseased, excision of the superior conjunctival fornix, the tarsus, or even the entire eyelid was practiced (Figure 3). For corneal pannus, a favored operation was 360° peritomy or peridectomy at the limbus, followed by application of a caustic agent to cauterize the blood supply to the pannus.

Although trachoma was recognized in the United States by the end of the 19th century, it was not systematically studied and addressed until early in the 20th century. The area in which trachoma was endemic was called the trachoma belt and consisted of a central region extending through Virginia, West Virginia, Kentucky, Tennessee, Missouri, Arkansas, Alabama, Oklahoma, and smaller contiguous parts of neighboring states. Surveys of the population of that area showed that approximately 2.5 to 7% of children and 12% of adults had some evidence of trachoma. In 1913, the Public Health Service was authorized and funded to systematically combat the disease.

The American Indian reservations were an area in which trachoma was epidemic. In 1912, the Public Health Service attempted to determine the prevalence of this disease among the various American Indian tribes, and this large investigation showed that trachoma was “a veritable scourge among the Indians.” The results of this study of many reservations showed that 23% of all Indians examined were trachomatous, and in the reservation’s boarding schools, 30% of the children were infected. In Oklahoma, 69% of all Indians were trachomatous, and in one boarding school, 92% of the children were infected. The overall incidence of trachoma among the Navajo Indians was 20% to 35%. The United States government, realizing the severe problem of disease among the Indians, established the Indian Medical Service under the Department of the Interior as the first permanent medical service on the Indian reservations.

What events led to the discovery of the first specific treatment of trachoma? The innumerable irritating and tedious medical therapies and the ingenious but painful and disfiguring surgical maneuvers were abandoned in 1938, when one of the world’s pioneer trachomatologists, Fred Loe, MD, introduced the use of sulfanilamide as the standard therapy for trachoma (Figure 4). He is a rarely acknowledged hero regarding this disease, having only been remembered at length in his obituary in the American Journal of Ophthalmology, written by Phillips Thygeson, MD, in 1966 and briefly discussed in an article about the history of trachoma in the United States, published in 2002. Loe’s work is also recounted in a history of the medical services on the Indian reservations. Surprisingly, Loe is not mentioned in the encyclopedic volumes by Duke-Elder or the definitive text about trachoma by Hugh Taylor. One of the most unusual aspects of Loe’s career was that he had no formal training in ophthalmology and was completely self-taught in this specialty.

The major source of information regarding his life is a letter from his widow, Bertha E. Loe, to Dr Thygeson, dated January 12, 1966, and sent after her husband’s death (G. Richard O’Connor, MD, written communication, May 2003). Thygeson seems to have closely followed the contents of this letter in writing Loe’s obituary. Thygeson’s
professional and personal friendship with Loe is recounted in this obituary and briefly discussed in his oral history for the American Academy of Ophthalmology. The archives of the Office of Indian Affairs of the Department of the Interior have been a rich source of unpublished information and pictures (Alan J. Dellapenna, Jr, Office of Public Health Support, Indian Medical Service, written communication, July 2009). This article also contains unpublished information from Loe's descendants (Fred A. Loe, DDS, written communication, September 2009). Other sources include the archives of the Proctor Foundation in San Francisco and contemporary literature regarding the discovery of sulfanilamide.

Fred Loe was born near Princeton in Mercer County, Missouri, on May 13, 1884. His family was poor, and it was necessary for all members, even Fred, the youngest of 5 children, to work on the neighbors' farms as well as their own. While still a boy, Loe would often accompany the local physician on his rounds and would read his medical texts. At that time, Loe decided to become a physician. After high school and college in Kansas City, Missouri, he attended the St Louis College of Physicians and Surgeons. Because little money was available to pay for his education, he practiced strict economy and had a job selling shoes at a big department store. He later remembered that the store manager had offered him a permanent job as a salesman, promising that it would be more lucrative than being a physician. In addition to that job, Loe also played professional baseball for 2 years, taking his medical books with him and saving his pay for his medical school expenses. He graduated from medical school in 1908 and served his internship at the St Louis City Hospital. Soon applied to and was accepted for a position with the Office of Indian Affairs. He served as a medical officer at several Indian reservations in Arizona, New Mexico, and South Dakota and then served in Minneapolis as part of the Trachoma Eradication program of the Indian Medical Service. Loe's medical practice was by no means limited to ophthalmology; he also served as a general medical physician.

In 1944, he retired from the Indian Medical Service after approximately 30 years of service and opened his own office for the private practice of ophthalmology and otolaryngology in Gallup, New Mexico. At this time, he was 60 years of age; he maintained a heavy clinical schedule until he retired at age 72. He then moved to Albuquerque, where he attended a radio operator school, passed his examinations, and became a ham radio (amateur radio) operator. With these skills, he became the first Albuquerque physician to participate in the Eye Net, a national ham radio network designed to transmit information regarding the need for and availability of corneas for transplantation. He continued to work at an eye clinic on the reservation of the Zuni tribe, where he was apparently the first physician to recognize the high incidence of myopia, astigmatism, and albinism in this population; he presumed this incidence occurred because of intermarriage in this tribe. Loe died in Albuquerque, New Mexico, on December 19, 1965, at age 81.

Loe's discovery of the curative property of sulfanilamide happened in the following manner. Loe first met Thygeson at a conference at the Fort Apache Trachoma Research Laboratory in 1937. Thygeson, who was impressed with Loe's knowledge of the ocular problems of the Indians, asked him to join with Francis Proctor, MD, and Polk Richards, MD, on a visit to New York for rounds and discussions of trachoma. Thygeson at that time was a professor at Columbia University. Together, they attended a lecture by a professor of bacteriology named Alphonse Dochez, MD, who reported that he had cured a case of distemper in dogs with a newly introduced drug, sulfanilamide. It was thought at that time that dog distemper was a viral disease, so the conclusion was that sulfanilamide would be efficacious as a treatment of viruses. After reviewing the scientific literature regarding sulfanilamide, Loe, assuming that trachoma was a viral disease, became excited and decided to try this new drug to treat his patients. He returned to the Sioux Reservation in South Dakota, and in August of 1937, he instituted topical therapy
by dusting sulfanilamide powder into the eyes of patients in addition to systemic therapy. His first treatment was limited to 2 patients, both with longstanding trachoma. After just 5 days of therapy, significant improvement was noted, and both were cured within a month without experiencing recurrence. Loe then extended his treatment to 140 other patients with equally gratifying results, obtaining a 90% cure rate.12

It is worth noting that Loe’s discovery was based on the then-prevalent theory that trachoma was caused by a virus. We now know that the infectious agent of trachoma is Chlamydia trachomatis, a small Gram-negative bacteria. We also know that Dochez’s dogs did not have viral distemper but a bacterial disease. Thus, Loe’s important breakthrough in medical science was based on 2 errors.11

Loe was one of several physicians who had noted the curative properties of sulfanilamide for trachoma during this period. In 1937 and 1938, the latter being the same year that Loe published his results, several reports by different investigators from the Dutch East Indies were published in a medical journal from Batavia (now known as Jakarta).13 This information probably was not known to Loe or other American investigators because those articles were published in Dutch in an obscure journal. Loe’s verbal presentation on June 15, 1938, to the Section of Ophthalmology of the American Medical Association convention in San Francisco and its publication in JAMA in October of that year was the main impetus for the worldwide medical community’s use of modern pharmacologic treatment for trachoma.12

Loe developed a standard course of treatment: oral sulfanilamide in a dosage of one-third grain per pound of body weight for the first 10 days and one-fourth grain for the next 14 days, followed by a lower dosage if indicated. Topical application of the drug did not prove to be as useful. This regimen was considered the standard for many years. Loe’s discovery was immediately recognized to be a major breakthrough in therapy for trachoma and was not only published in JAMA but also reprinted in the specialty journal Transactions of the Section on Ophthalmology.12

Loe worked with pharmacologists to try to standardize the dosages of sulfanilamide by measuring the level of the drug in the blood of patients. With regard to complications, few serious adverse effects were noted. Many of the patients reported headaches, dizziness, vertigo, and nausea at first; these complications disappeared for most patients. A few were noted to have cyanosis that required discontinuation of therapy, and a few had skin reactions.12

Loe’s results were almost immediately confirmed by many other investigators. At the same meeting in which Loe presented his initial data, Harry Gradle, MD, from Chicago, also spoke. He had been informed of Loe’s report to the Department of the Interior and had begun treatment of patients with trachoma in Chicago and in the trachoma clinics in southern Illinois. He noted that oral sulfanilamide treatment without topical therapy for 3 weeks produced impressive subjective and objective improvement in almost all cases of acute trachoma.12 A year later, Loe’s results were confirmed on the Indian reservation at Fort Apache by Richards, Forster, and Thygesson,14 whose impression was that “the therapeutic effect of sulfanilamide was beyond question.” They noted that the epithelial cell inclusions found in conjunctival scrapings from 13 of their 14 trachomatous children before the start of therapy could not be demonstrated after sulfanilamide therapy and that the epithelial secretions from treated patients were no longer infectious when inoculated into the eyes of baboons.19

Because these early studies demonstrated such marvelous results, the Office of Indian Affairs began a nationwide trachoma treatment program. Its success on the Indian reservations was miraculous. The campaign was costly, requiring the services of physicians trained in trachoma control and a corps of nurses who specialized in treatment of the disease. Loe, with his intimate knowledge of the Indian way of life, was instrumental in developing mass educational campaigns to accomplish this mission. The success was greatest in Indian boarding schools in which all children could be treated; the coverage of the adult population was insufficient to totally eradicate the disease. Loe noted that between 1937 and 1941, the incidence of trachoma was reduced from 26% to 3.6%.15 Other investigators noted that 75% of patients were cured with 1 course of treatment and that 90% were cured with a larger dose of sulfanilamide, although the standard course of therapy was 3 weeks.16

However, the campaign was prematurely halted because of the onset of World War II and because sulfanilamide was requisitioned for military use. Loe was unable to persuade the Indian Bureau to maintain proper screening and treatment during the war years. As a result, trachoma rebounded to approximately its prewar levels in the Navajo, Apache, and Pima tribes. After the war ended, an outbreak of trachoma on a reservation in Arizona was discovered, with 35% of children infected; as late as 1955, the incidence of trachoma among the American Indians was 560-fold more common than in non-Indians. As a result, the entire program was reinstated by the Public Health Service, and finally trachoma was eradicated in the Indian reservations by the 1970s (Figure 5).17

Loe also demonstrated that topical sulfanilamide application would prevent ophthalmia neonatorum. He noted that sulfanilamide was prophylactic against inclusion body conjunctivitis and gonorrheal ophthalmia.15 He commented that sulfanilamide was
a stable drug, maintaining its strength for an indefinite period, in contrast to unstable silver nitrate solution, which required compounding at frequent intervals (Fred Loe, MD, unpublished letter to the Commissioner of Indian Affairs, April 14, 1946).

Clearly, the introduction of sulfanilamide was a huge advance in the arsenal of therapy for trachoma. It rendered all prior therapies obsolete except surgical correction of chronic cicatricial eyelid disease and corneal scarring. The present program to eradicate trachoma uses the SAFE strategy, with S standing for eyelid surgery to correct entropion and trichias, A for antibiotics to treat infectious trachoma (azithromycin is now the drug of choice), F for personal hygiene and cleanliness, and E for environmental hygiene and cleanliness.

In 1997, the World Health Organization established the Alliance for Global Elimination of Trachoma by the year 2020. Progress to reduce trachoma has been successful, with the incidence of affected persons reduced from approximately 500 million in the 1980s to approximately 40 million as of 2009. With sustained funding and political will, it may be possible to eradicate trachoma as a cause of widespread blindness.

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