James Wardrop should be remembered not only as one of the founders of ocular pathology but also for his contributions to the field of comparative ophthalmology. He described a “specific inflammation” that veterinarians today know as equine recurrent uveitis. As described by Wardrop in the 19th century, this condition is known today to eventually lead to blindness.

In 1782, James Wardrop was born in Linlithgow, Scotland, a small township near Edinburgh (Figure 1). He had extensive training as a general surgeon, and by the age of 22 years had completed a 4-year surgical apprenticeship in Scotland; a 2-year appointment as house surgeon in London, England; part of a year at a prestigious Paris, France, medical school; and a year under Georg Joseph Beer in Vienna, Austria. Beer had established the first clinic limited to the practice of ophthalmology in Europe some 17 years earlier. In 1823, Wardrop was appointed Surgeon Extraordinary to the Prince Regent, who later became King George IV. Wardrop’s reputation as one of the foremost surgeons in his day, however, rested more on the accuracy of his diagnoses, his ability to be an original and forceful thinker, and the number and value of his publications rather than on his technical skills.1

Although Wardrop was considered a general surgeon, his greatest contributions included establishing the foundations for ophthalmic pathology and being the first to classify ocular diseases according to the anatomical parts involved.2 One may speculate that at least some of his interest in ophthalmology was fostered by his having an exotropic left eye as a child. He coined the term keratitis. He also had a passion for hunting and horse racing and was considered “one of the best judges of horses in the Kingdom.”3 In 1819, he combined his fascination for ocular pathology with his extensive knowledge of horses in An Essay on the Diseases of the Eye of the Horse.4 This important work helped to build a foundation for equine ophthalmic anatomy and aided in the differentiation of inflammatory diseases of the equine eye based on the tissue of origin. More specifically, the essay is notable be-

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cause it is among the first to differentiate a form of ocular inflammation that Wardrop termed specific inflammation from other forms of ocular inflammatory disease in horses. Today this condition is called equine recurrent uveitis (ERU), and it affects 10% to 15% of all horses, making it the leading cause of blindness in horses then and now.\(^3\) The essay is also noteworthy for its allusion to the notion of sympathetic inflammation between the 2 eyes and its description of several surgical techniques for treating ocular disease in horses, including the use of glass eyes to prevent deformity in horses that have lost an eye.\(^3\)

Wardrop’s interest in equine ophthalmology appears to stem from the critical economic role horses played in his day, his innate scientific curiosity, and an aesthetic appreciation for the animal’s strength and beauty. In 19th-century Georgian society, human productivity and physical safety were heavily dependent on the animal having good vision. Wardrop recognized that chronic ERU was the most common cause of visual loss in horses and, hence, was of great economic importance, because it often rendered the animal useless for its intended purpose and sometimes bankrupted its owner in the process. However, Wardrop was also insightful because as a physician-scientist, he saw human and veterinary medicines as a single medicine in which a better understanding of the diseases of one species would benefit the other, and vice versa. Although he erroneously believed horses had fewer and more uniform ocular diseases than humans\(^4\) (perhaps in part because horses have a much more florid inflammatory response than do humans), his appreciation for the linkage between species allowed him to make significant contributions to both human and veterinary medicine. It was also Wardrop’s hope that differentiation between the various types of ocular inflammation based on anatomy would facilitate improving the selection and breeding of quality animals.\(^4\)

In An Essay on the Diseases of the Eye of the Horse, Wardrop elucidated 2 principal forms of ocular inflammation.\(^4\) The first form, which he called simple or common inflammation, was a keratoconjunctivitis that was characterized by swollen eyelids, conjunctival hyperemia, ocular discharge, and diffuse or focal loss of “pellucidity and lustre” of the cornea.\(^7\) In advanced stages, corneal perforation and loss of “appearances and utility” of the eye occurred.\(^4\) The critical observation, however, was that anterior uveitis was secondary to corneal disease. Systemic signs such as fever, loss of appetite, thirst, “frequency of the pulse,” unhealthy appearance of the coat, and alternate “heat and chills” often accompanied this form.\(^4\) Trauma was a common cause, but it was also seen as a consequence of colds and fevers. Young horses and those in “high condition” were more commonly affected,\(^4\) as they were under the greatest amount of stress. We can assume by “high condition” he meant horses that were used for racing purposes and, hence, may have also been more commonly treated because of their value.

Today’s veterinary ophthalmologist would easily recognize the patients that Wardrop describes, and in addition to traumatic keratitis would include as possible causes sterile corneal stromal abscesses, corneal foreign bodies, bacterial keratitis (especially due to Streptococcus species, Staphylococcus species, Acinetobacter species, and Pseudomonas species), fungal keratitis (due to Aspergillus species and Fusarium species), viral keratitis (equine herpesvirus 2, equine influenza virus A\(_2\), and adenovirus), ocular parasites such as Onchocerca cervicalis and Thelazia species, and allergic and chemical irritations.\(^5-10\) The similarities between these causes and those seen in humans are striking and speak to the validity of Wardrop’s concept of applying medical principles across species lines.

Although the methods of treating these disorders have improved greatly from the “bleeding, purging, and blistering” of Wardrop’s day,\(^4\) he recognized that the outcome often depended on the immediate and aggressive treatment of the inflammation if the course of the disease was not to be protracted or to result in long-term damage to the globe. As today, he also recognized the importance of “paying attention to the air of the stable; for this is often impure.” In addition, he recommended avoiding exposure to light and not feeding the animal a large amount of grain.\(^4\) Modern equine medicine has recognized that housing in a stable increases fungal contamination of the equine conjunctiva\(^10\) and that sunlight induces intense ocular pain and photophobia in horses with keratitis. Wardrop correctly argued against a common practice at the time of scarifying the eyes and removing the third eyelid, although in some circles in the United States this unfortunate practice persisted until well into the 1900s. He advocated extreme caution in draining a hypopyon and emphasized careful surgical technique when doing so.\(^4\) Today, rather than trying to treat an obvious clinical sign of the condition (eg, ocular surface vascular injection) by limiting ocular blood flow by means of therapeutic bleeding and inducing systemic hypotension with purgative balls, the veterinary ophthalmologist uses many of the same antimicrobial agents familiar to the physician, along with systemic and topical anti-inflammatory medications.

Wardrop was among the first to clearly differentiate in horses the primarily corneal origin of simple inflammation from the uveal origin of the second form of ocular inflammation that he called specific inflammation.\(^4\) Although the 2 forms appear superficially similar, the latter has more serious consequences for vision and is the “most dangerous disease of the Eye of the Horse.” Unlike the corneal origin of simple inflammation, he noted that the uveal origin of specific inflammation was also more frequent in “particular lines of blood.”\(^4\) This observation was later borne out in studies that found certain horse breeds such as the Appaloosa to have an 8-fold increased frequency of ERU.\(^3\) It affected animals of all ages, all classes, and all states of condition, although horses that were “high bred” or in high condition were believed to be more commonly affected. Dark, ill-ventilated stables were thought to have a great influence on the incidence of the disease.\(^4\)
Wardrop noted that specific inflammation usually develops very suddenly, that it is characterized by swelling of the eyelids and copious tearing, but that the conjunctival injection is not as great as in simple inflammation.\(^4\) A key differentiating feature, however, is lack of a “distinct speck on the cornea,” and the whole anterior chamber is “dim and clouded.”\(^4\) As in simple inflammation, this form may exhibit varying degrees of hypopyon.\(^4\) The condition is often, at least initially, unilateral and may be quite asymmetrical in severity. He described spontaneous resolution of the inflammation over a period of a few weeks and observed that the eye may then look quite normal or may have adhesions that distorted the pupil (posterior synechia). He astutely noted that inflammatory episodes typically recur at varying and sometimes quite distant intervals, and that ultimately the accumulated damage leads to a cataract and visual loss.\(^5\) Well before the introduction of the ophthalmoscope in 1850,\(^13\) Wardrop described dissecting the eyes of these horses and finding a collection of fluid “between the choroid coat and retina,” condensation of the vitreal elements, and a retina that is detached and compressed “into a chord or bundle.”\(^5\) Finally, as some of today’s horse buyers can still attest, Wardrop marvelled at how astute some dealers in horses were in identifying horses that have had an episode of specific inflammation and how the dealers would sell an animal (often during a period of quiescence) before the animal’s value was lost owing to blindness.\(^4\)

As with simple inflammation, Wardrop’s description of specific inflammation is easily recognized by today’s veterinary ophthalmologist. It is most commonly known as ERU but has also been referred to as periodic ophthamalia, recurrent iridocyclitis, relapsing uveitis, and “moon blindness.” The latter term purportedly originated with Vegetius in the fourth century AD, who thought that the cyclic nature of the inflammatory outbreaks was associated with changes in the phases of the moon.\(^18\) In Wardrop’s essay, he diverged from this traditional use of the term moon blindness and instead used it to describe a dense white cataract that perhaps resembles a brightly illuminated moon. Nevertheless, his description of recurring bouts of epiphora, photophobia, anterior chamber opacification, ocular vascular injection, and the visually devastating sequelae of synechiae, cataract, and retinal detachment could be easily found in today’s textbook descriptions of horses with ERU (Figure 2 and Figure 3). With the comparatively recent advent of tonometers such as the Mackay-Marg and Tono-Pen (Mentor Ophthalmics, Norwell, Mass) that are suitable for use in horses, glaucoma also has been found to be a sequelae of ERU.\(^19\) Equine recurrent uveitis is the most common cause of glaucoma in horses, although glaucoma itself is relatively uncommon in horses, perhaps because of their very large uveoscleral outflow pathway.\(^20\)

Today ERU is regarded as an umbrella term for a diverse set of diseases characterized by episodes of active uveitis alternating with varying intervals of clinical quiescence.\(^8\) It undoubtedly remains one of the leading causes of blindness in horses worldwide.\(^3,8\) The typical initial episode consists of severe anterior uveitis, but subsequent episodes are less severe and more chronic in nature. Ultimately, the accumulated ef-
fects of the inflammation lead to progressively more destructive pathologic changes and visual loss. Causes believed to be important today include the spirochetes *Leptospira interrogans* and *Borrelia burgdorferi*; other bacterial infections that include *brucellosis, salmonellosis, streptococcus hypersensitivity, Escherichia coli, and Rhodococcus equi*; the parasites *Onchocerca cervicalis, Toxoplasma gondii*, and various other intestinal parasites; and viral agents that include equine influenza virus, equine herpesvirus 4, equine arteritis virus, and possibly equine anemia virus. In addition, blunt or penetrating trauma may play an inciting role by breaking down the relatively labile equine blood-aqueous barrier. Wardrop’s admonition to consider the environment proved to be prescient, since it is clear that many of the infectious causes of ERU in horses are acquired through less-than-optimal husbandry practices. Again, the striking similarities between the recognized causes of ERU in horses and the causes of uveitis in humans speaks to Wardrop’s insight into comparative ophthalmology.

The pathophysiology of ERU is unclear, but the disease undoubtedly has an immune-mediated basis. It has been speculated that a common theme of all of these inciting causes is that they disrupt the relatively unstable blood-aqueous barrier of the equine eye and allow immunologically reactive components to enter the eye. Hypersensitivity to *L. interrogans* serovars (especially *pomona*) is commonly implicated as a cause, and the equine cornea and lens have been shown to share antigenic properties with this organism. Although anti-*Leptospira* antibodies are found in the serum, tears, and aqueous humor of horses infected with *Leptospira*, living organisms are not necessary for ERU to occur. Frequently, uveitis may not be seen until 15 months after systemic infection with *Leptospira*, and the fact that it can resolve with only anti-inflammatory drugs again suggests that it is primarily immune-mediated in nature.

Although horses that are seropositive for antibodies to *L. interrogans* serovar *pomona* are 13.2 times more likely to have uveitis than seronegative horses, not all seropositive horses will develop uveitis. This finding, in conjunction with the recognized heritable nature of ERU, has led some to suggest that ERU in horses occurs in a manner analogous to that in humans who possess the tissue marker HLA-B27 and develop uveitis in association with *Klebsiella* species. That is, uveitis develops only if the horse possesses an as yet undefined specific tissue antigen and is also exposed to *L. interrogans*. Nevertheless, a significant number of horses with uveitis are seronegative to all serovars of *L. interrogans*, indicating that this organism alone is not the sole cause of ERU in horses.

The histopathological changes in ERU have built on Wardrop’s descriptions, and today ERU is characterized as a uveal lymphoplasmacytic inflammatory infiltrate that most commonly affects the nonpigmented ciliary epithelium of the ciliary processes. Other histologically identifiable lesions involving the nonpigmented ciliary epithelium include linear eosinophilic intracytoplasmic inclusions that may be located within mitochondria and thick acellular hyaline membranes closely adherent to the inner aspect of the nonpigmented ciliary epithelium (Figure 5). In patients with chronic ERU undergoing an acute episode, a perivascular lymphoplasmacytic inflammatory infiltrate within the choroid, retina, optic nerve, and anterior uveal tract is often identifiable. An exudative retinal detachment may result from the chorioretinitis. These retinal detachments may focally reattach because of fibrous organization or may progress to total separation. Vitreous opacities, chorioretinitis, retinal detachment, and optic nerve atrophy are frequently observed in chronic ERU (Figure 6).

Although Wardrop viewed specific inflammation as usually incurable, he thought there was some benefit from bleeding (≤2.9-4.8 L from the jugular vein closest to the affected eye), administering purgative balls, feeding a “cooling diet” (less high-energy feedstuffs such as grain), and improving the ventilation of the stable. Given that ERU frequently resolves spontaneously (at least initially), and that chronic forms may require slitlamp biomicroscopy to identify that they are active, it is highly likely that many treatment strategies—perhaps even those used today—are erroneously believed to be effective. He also applied a “vinous tincture of opium” with a brushlike camel’s-hair pencil to the globe 2 to 3 times daily, meaning he applied medicine that stained the eye, using a whisker-like instrument for its application.
He believed that this procedure was helpful in some cases, although the real value of this therapy may simply have been to provide some degree of pain relief.

Of interest is Wardrop’s observation that, as in humans, ERU is often initially unilateral. He questioned whether destroying the first eye would arrest the progress of the disease in the fellow eye, and so he treated a valuable race horse with unilateral disease by incising the cornea and expressing the lens, vitreous, and other intraocular contents. He reported that the animal did not experience an episode in the opposite eye for up to 6 years later. He noted that others before him used less refined techniques for destroying the diseased eye such as putting quicklime between the eyelids or by thrusting a nail into the eye in hopes of preventing the disease in the opposite eye. Obviously, such therapy would be considered cruel today.

Although there is some suggestion that severe ERU might allow the exposure of immunologically isolated antigenic constituents such as interphotoreceptor retinoid-binding protein or retinal S antigen and, hence, could result in disease in the contralateral eye, to date no study has demonstrated a benefit to destroying the affected eye; in addition, the histological changes seen in ERU are not consistent with sympathetic ophthalmia. Currently, ERU is not regarded as a variant of sympathetic ophthalmia but instead as a disease that often affects both eyes asymmetrically. The slitlamp microscope, a tool not available to Wardrop, has allowed the detection of low-grade inflammation in the fellow eye of a substantial number of horses that have what appears to the naked eye to be unilateral disease.

Today’s veterinary ophthalmologist uses many of the same medications that the physician uses to treat humans with recurrent uveitis. Because it may be difficult to safely approach the eye of a very large animal that has considerable ocular pain, a subpalpebral lavage system is occasionally placed to facilitate treatment of fractious animals. This system consists of a tube that is placed into the dorsal or ventral conjunctival fornix and out through the skin of the upper or lower lid, respectively. This tube connects with a port that is secured near or through the mane of the horse and allows medication to reach the corneal surface safely through the opening in the fornix. The treatment of ERU is also complicated by the fact that even topical atropine sulfate can induce gastrointestinal tract stasis and colic (which can be fatal to large herbivores), and that systemic corticosteroid therapy may result in the keratinized hoof separating from the underlying bone (laminitis), thereby potentially permanently crippling the animal. Recently topical and intravitreal cyclosporine (administered as a sustained-release intravitreal implant) has shown promise in reducing the severity of the disease and the frequency of attacks. Although pars plana vitrectomy has been suggested as another avenue to prevent recurrent episodes, this approach requires longer-term follow-up and replication at other centers before it can be widely advocated.

Figure 5. Photomicrograph of a portion of the ciliary process in a horse with equine recurrent uveitis. Linear eosinophilic intracytoplasmic inclusions are located within the nonpigmented ciliary epithelium (NCE) (arrows). Lymphoplasmacytic inflammatory infiltrate affecting and internal to the NCE is seen (Masson trichrome, original magnification ×400). (Digitally processed image.)

Figure 6. Fundus photograph of a horse with a classic, peripapillary “butterfly” typical of equine recurrent uveitis. The winglike altered fundus reflectivity on both sides of and inferior to the optic disc represents previous chorioretinitis. Wardrop did not describe such lesions, as his observations were made before the origin of the ophthalmoscope. (Digitally processed image.)
As evident, our understanding of ERU has come a long way since James Wardrop differentiated between the various forms of ocular inflammation in the horse. Nevertheless, ERU remains the most common cause of blindness in horses, and much more needs to be done if we are to address the economically important and aesthetically disfiguring condition effectively. Unfortunately, despite potent modern immunosuppressive drugs and broad-spectrum antibiotics, today’s veterinary ophthalmologist would have to agree with Wardrop’s observation in 1819 that “however beneficial these remedies may ever be, their efficacy always seems to be lessened by the repetition of attacks, and the ultimate destruction of the organ.”

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