Experimental chronic uveitis
Ophthalmic signs following equine leptospirosis

R. D. Williams,* R. L. Morter, M. J. Freeman, and A. M. Lavignette

The present study was conducted as the first phase of an investigation of the pathogenesis of equine uveitis. Two groups of Shetland ponies were exposed to leptospires and subsequently proved to have been infected. Weekly ocular examinations and fundic photography were used to study the development of lesions and to establish their role in the genesis of equine chronic uveitis. Exacerbations during the experiment were sporadic and resulted in varying degrees of ocular damage. Alterations in 22 clinically affected eyes (61 per cent) included synechiae, pigment rests, lens and vitreal opacities, and focal and peripapillary lesions. The pathogenesis of the fundic lesions, seen in 19 of the eyes, is discussed in relationship to the unique vascular patterns of the equine eye.

Key words: chronic uveitis, leptospirosis, equine, ophthalmic observations

The occurrence of ocular lesions in man following clinical, systemic leptospirosis was first reported in 1886 in Weil's original description of leptospirosis. Subsequently, in 1949, 222 documented human cases were reported in which uveitis developed as a late sequela to leptospiral infection. The incidence of this ocular involvement has been estimated to vary from ten to 40 per cent. Lesions may develop as early as two weeks or as late as one year following the systemic manifestations of infection, but iritis, chorioretinitis, and/or iridocyclitis usually appear within one to six months.

A correlation between chronic uveitis (recurrent iridocyclitis), the most important ocular disease of horses, and leptospiral infection was suggested initially by Rimpau and later widely substantiated by the demonstration of leptospiral agglutinins in the sera of affected horses. In one carefully studied instance of naturally occurring Leptospira pomona infection of horses, ophthalmitis developed 12 to 24 months after acute illness. The relationship between leptospirosis and equine uveitis was further substantiated by development of uveitis in all of nine Shetland ponies 12 to 14 months after experimental infection. Histologically, the lesions were
Experimental chronic uveitis

nongranulomatous and characterized by an abundance of lymphocytes and plasma cells.9

Clinically, equine chronic uveitis is characterized by recurring acute attacks which are separated by periods of apparent quiescence. Exacerbations may persist for several days to several weeks. The initial signs of an exacerbation include lacrimation, photophobia, blepharospasm, congestion of the conjunctival and episcleral vessels, interstitial keratitis, and decreased intraocular tension. Signs of pain may be elicited by global palpation. Progressively, the blepharospasm becomes more pronounced and, secondarily, the lacrimal discharge becomes purulent. Exudates appear in the anterior chamber, and vitreal opacities and capsular cataracts may be detected. Persistent lesions may develop following one or more exacerbations. These include: anterior or posterior synechia, pigment rests on the anterior lens capsule, iridial atrophy, corneal, lenticular or vitreal opacities, persistent corneal vascularization, and phthisis bulbi. Blindness may develop after several attacks.10-X1

Since very little detailed information on the progressive ocular changes was available, the present study was conducted as the first phase of an investigation of the pathogenesis of equine uveitis. Two groups of Shetland ponies were exposed to leptospires and subsequently proved to have been infected. Control ponies were inoculated subcutaneously with 2.5 ml. of normal guinea pig blood.

Preparation of inoculum. Principals were inoculated subcutaneously with about 10⁵ organisms of the Wickard strain13 of L. pomona contained in 2.5 ml. of heparinized blood obtained from febrile guinea pigs after five serial passages of leptospiromic blood. Control ponies were inoculated subcutaneously with 2.5 ml. of normal guinea pig blood.

Microbiologic procedures. Hemocultures for the detection of leptospiromia were prepared three to ten days after inoculation by inoculating Stuart,14 Chang,15 or oleic acid albumin complex16 medium with three to five drops of blood obtained by jugular venipuncture. All cultures were incubated at 27 C. and examined weekly by dark-field microscopy for five weeks or until leptospires were detected.

Intraperitoneal inoculation of 2 ml. of freshly collected urine into each of five guinea pigs or inoculation of several drops of urine into Fletcher medium14 containing 100 µg of 5-fluorouracil per milliliter19 was used to detect leptospiruria. The detection of viable leptospires in the culture medium or the appearance of leptospiral agglutinins in sera of the inoculated guinea pigs 18 to 21 days after inoculation was considered to prove the presence of leptospires in the urine. Serum agglutinin titers were determined by the microscopic agglutination test with live L. pomona as antigen.17

Results

Demonstration of leptospiral infection. A febrile response of two to three days’ duration, with rectal temperatures of 102.8 F. to 104.6 F., was detected as early as three and as late as nine days after inoculation. Leptospires were isolated in hemoculture from all ponies of both groups (Table I). Infection was also substantiated by detection of serum agglutinins at six, seven, and eight days after inoculation. Peak levels of leptospiral agglutinins oc-
Table I. Hemocultures of ponies following inoculation with *L. pomona* (Exp. 1)

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DAI = day after inoculation; + and 0 = positive and negative hemocultures. Similar results were obtained for Exp. 2.

Table II. Microscopic agglutination titers of pony sera after experimentally induced leptospirosis (Exp. 2 ponies)

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Titer expressed as the logarithm (to base 10) of the reciprocal of the greatest serum dilution with 50 per cent or more agglutinated leptospires. Similar results were obtained for Exp. 1. DAI and WAI = day or week after inoculation, respectively.

The signs and course of uveitis for an eye from a single pony that became blind are described. No detectable changes occurred prior to 50 weeks after inoculation, at which time the fundic vessels suddenly became obscured by vitreal haziness. The external and anterior segments of the eye remained normal during the next 18 weeks, but a progressive increase in cloudiness of the vitreous and lens was observed. At 69 weeks after inoculation, another exacerbation characterized by severe miosis, lacrimation, photophobia, and iris bombé occurred. A fibrous exudate on the anterior surface of the iris, aqueous flare, and increased opacity of the lens were observed. A slight regression of clinical signs was followed by a severe exacerbation at 75 weeks after inoculation which was characterized by deep interstitial keratitis, lamination, and miosis. Iritis accompanied the development of a large, fibrinous mass in the inferior aspect of the anterior chamber. By 76 weeks after inoculation, the keratitis had intensified and posterior synechiae were evident. Regression of the iritis and keratitis and absorption of the fibrinous mass occurred in the subsequent two weeks. Five weeks later (81 weeks after inoculation), the pupillary margins were irregular and pigment rests were present on the anterior lens capsule and the lens opacity had increased. Mild exacerbations occurred during 88 and 98 weeks after inoculation, resulting in increased lens opacity and numerous pigment rests. Clinically similar exacerbations occurred at about 107 and 115 to 119 weeks after inoculation. During regression (119 to 146 weeks after inoculation) new pigment rests and increased lens opacity became apparent. The results of these several exacerbations were phthisis bulbi, a persisting discoloration of the iris, an opaque lens, multiple pigment rests on the anterior lens capsule, vascularization of pigment rests from...
adjacent posterior synechiae, and an irregularly shaped pupil. The lesions of six other eyes developed in a similar progressive manner, but the number and severity of exacerbations varied.

The changes in five of 29 less severely affected eyes included lens opacities, pigment rests on the anterior lens capsule, varying periods of miosis and epiphora, the sudden appearance of fibrin clots in the anterior chamber which slowly resorbed, and several types of fundic changes. Six eyes developed progressive lesions and nine developed lesions that remained static.

**Fundic observations.** Approximately 18 (56 per cent) of the eyes which did not become blind had definite peripapillary lesions. Fig. 1 shows a normal equine fundus. Fundic lesions in affected eyes were generally confined to the nontapetal region (Fig. 2), although they sometimes extended into the tapetal fundus. The lesions were irregular in shape, lacked pigment, were reddish or yellowish in color, and usually were very distinct from the surrounding pigmented nontapetal area. Lesions observed were unilateral or bilateral and located either temporally or nasally to the optic disc. In many instances lesions were nearly circumpapillary, leaving either a superior or inferior area unaltered. The papillary margins were indistinct in five eyes (Figs. 3 and 4). Discrete, proliferative, pigmented foci were scattered throughout the unpigmented peripapillary lesion in several eyes.

Focal lesions, not adjacent to the optic papilla, were seen in seven eyes. These areas, located in the nontapetal region, were focal, discrete, irregularly round pale-gray spots, and occurred singly or in groups (Fig. 5). Some foci contained pigment. The slow progression of the fundic changes was best observed by comparing photographs taken at intervals of weeks or months.

**Discussion**

The relationship between leptospirosis and chronic uveitis has been well documented on the basis of clinical, serologic, microbiologic, and experimental evidence. 6, 7, 8 Acute exacerbations of the disease are self-limiting but frequently recur. The lesions, characteristically located in the iris and ciliary apparatus, consist primarily of lymphocytic and plasma cellular infil-
Fig. 3. Marked alterations in the tapetal vascular pattern with development of collateral circulation. Margin of the superior border of the optic papilla is indistinct and papillary vessels appear enlarged and tortuous (113 weeks after inoculation).

Fig. 4. Indistinct superior papillary border and alterations in fundic vascular pattern (90 weeks after inoculation).

A common early feature of the eyes that progressed to blindness in the present study was the development of vitreal cloudiness that obscured the fundus. This lesion may be associated with an increased protein content of the vitreous humor as a result of alterations in vascular permeability within the uveal tract. The accumulation of fibrin over the anterior iridial surface and in the aqueous fluid was a further indication of altered vasculature. It is known that vascular permeability may persist, in the absence of inflammation, for long periods of time. Increased uveal vascular permeability has actually been demonstrated with horses with uveitis by administration of dye intravenously. Dye accumulation in the fluid compartments of affected eyes is more marked and rapid than that in normal eyes. Thus, the early vitreal cloudiness may be the initial clinical indication of intraocular inflammation. Miosis, iridocycous, corneal vascularization, and increased protein content in the aqueous humor are all signs of ocular inflammation that may arise from the initial increased vascular permeability of the uveal tract.

The fundic lesions observed were similar
Monly been associated with chronic inflammation. In these areas, pigmented cells adjacent to the involved inflammatory site usually undergo hyperplasia and become several layers thick instead of the normal single layer of cells.

The basic vascular alterations of the uveal tract may be significant in the development of both the circumpapillary lesions and the discrete foci of chorioretinitis of equine chronic uveitis. Since the retinal vascularization is limited to a zone approximately 4 to 6 mm. wide around the optic papilla, the greater part of the retina is avascular. In the vascular peripapillary zone, the blood vessels do not penetrate deeper than the layer of nerve fibers. Thus, nearly all the retina is dependent upon the choriocapillaris for nutrition.

Damage to the choroidal vessels would alter the pigmented epithelium and would appear as areas of depigmentation adjacent to sites of hyperpigmentation. Comparisons of fundic photographs of the same eye at varying intervals revealed changes in the patterns of pigmentation and development of collateral circulation, suggesting that choroidal infarcts may have developed during acute inflammation.

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