THYGESON'S SUPERFICIAL PUNCTATE KERATITIS: NATURAL HISTORY AND ASSOCIATION WITH HLA DR3

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THYGESON'S SUPERFICIAL PUNCTATE KERATITIS (TSPK) IS AN EPITHELIAL KERATITIS with insidious onset, numerous remissions and exacerbations, and long duration (from several years to more than 30 years).[1-8] In the absence of a specific diagnostic test or known infectious agent, the diagnosis must be based entirely on clinical history, physical findings, and therapeutic response to corticosteroids. The classic epithelial sign is that of an oval-shaped, grouped punctate epithelial keratitis associated with little subepithelial edema or opacity.[6-8] However, grouped punctate epithelial keratitis may be absent when the patient is first examined and may be altered in character by the administration of topical corticosteroids or antiviral agents.[8] Smaller round or branched lesions may be the presenting sign and lead to an inappropriate diagnosis of herpetic keratitis. A diagnosis of TSPK can be made even in the absence of classic epithelial lesions if the patient has the appropriate long history with insidious onset, remissions and exacerbations, absence of conjunctival reaction, and response to topical corticosteroids. Classic epithelial signs are often observed later in the course of the disease during subsequent exacerbations. Thygeson[8] believes that subepithelial opacities are not part of the natural history of TSPK but a consequence of the use of topical antiviral agents; others[9,10] believe that subepithelial opacities can follow long-standing disease.

The purpose of this thesis is to review the literature concerning TSPK, to present the clinical characteristics of 36 unreported cases, to discuss the nature and specificity of the corneal lesions, and to report a highly significant association between TSPK and histocompatibility antigen HLA DR3. The HLA D and HLA DR antigens are associated with the immune response genes. The HLA DR3 antigen may alter the immune response of persons with TSPK to exogenous or endogenous virus infections, yielding the prolonged course and exacerbations and remissions characteristic of the disease.

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HISTORICAL REVIEW

In 1950 Thygeson[1] reported 26 examples of superficial punctate keratitis that he had been studying for 20 years. The lesions of this keratitis were multiple and discrete; there were as few as three to as many as 20, favoring the pupillary area and staining variably with fluorescein. Each opacity was made up of a group of smaller opacities that were intraepithelial, with little or no subepithelial edema and no subepithelial infiltration. The opacities were evanescent, often changing their location from week to week, although in some cases the pattern remained fixed for several months. Corneal sensation was normal. Mild catarrhal conjunctivitis of the bulbar conjunctiva accompanied the corneal lesions during exacerbations but was not associated with papillary hypertrophy of the tarsal conjunctiva. Typical symptoms were photophobia, foreign-body sensation, burning, tearing, and blurring of vision, and the disease was always bilateral. There was no sex incidence and the youngest patient was 8 and the oldest 65 years of age. No patient could give a clear-cut history of the exact time of onset of the disease, and the minimal time for healing was three years. Treatment by removal of corneal epithelium with the application of iodine or by repeated smallpox vaccination was helpful in half the cases so treated. Thygeson proposed naming this disease "superficial punctate keratitis," pointing out that while Fuchs had used the name 60 years earlier for what is now called epidemic keratoconjunctivitis, the term superficial punctate keratitis had fallen into disuse.

The same year, Braley[2] described one case of superficial punctate keratitis from which a virus had been isolated, and three years later Braley and Alexander[3] presented nine cases they had followed from four to eight years. The corneal lesions of these patients were bilateral, characterized by both epithelial and subepithelial opacities, oval in vertical axis, composed of tiny white or gray dots, and centrally located (although more commonly found in the upper half of the cornea). These cases differed from those of Thygeson because they presented a nearly uniform hyperemia of the blood vessels between the superior rectus and the superior corneal limbus. Braley described the life cycle of these epithelial lesions, which began as small epithelial flecks and became larger and oval, finally forming true filaments. Hyperemia of the superior bulbar conjunctiva in association with filamentary keratitis of the superior cornea is now considered to be superior limbic keratoconjunctivitis. Material from five corneal scrapings from a single patient were placed in embryo mouse brain tissue culture to obtain material for injection intracerebrally into brains of white mice, which in turn were used for further tissue culture and intracerebral transfer. A virus was isolated by this method that appeared to cause

corneal lesions in a rabbit similar to those seen in patients and to stimulate antibodies against the virus. Subsequent authors have suggested that this virus was a latent mouse virus.[7] Braley's report was the first to mention the value of topical cortisone in treating superficial punctate keratitis.

In 1959 Sugiura et al[4] presented five cases of superficial punctate keratitis. They proposed, however that this name be reserved for the corneal signs of epidemic keratoconjunctivitis and that the name keratitis punctata epithelialis be reserved for the disease described by themselves and Thygeson. The punctate epithelial opacities were raised in the center and composed of several smaller epithelial opacities. They were ellipsoid in shape but could present spindle or small round forms. With severe inflammation the epithelial opacity developed a raised center and was accompanied by subepithelial opacification to a depth of one fifth of the anterior stroma. All five cases treated with topical corticosteroids improved. Material taken from the third case was inoculated into monkey cornea; while subepithelial punctate opacities were observed four days after inoculation, no epithelial lesions appeared. They were not successful in isolating a virus in rabbit cornea or in HeLa, human, or suckling mice tissue cultures. They believed that the clinical entity could be characterized by the specific grouped punctate opacity of the epithelial cells of the cornea, complete recovery after relapses, normal corneal sensation, and only mild conjunctival inflammation.

In 1960 Jones[5] addressed the problem presented by the differential diagnosis of punctate keratitis. Under his classification of coarse punctate epithelial keratitis he placed (1) those conditions not associated with acute conjunctivitis, specifically Thygeson's punctate epithelial keratitis and (2) those conditions characterized by acute conjunctivitis, namely, the early stages of herpes simplex infection, varicella zoster infection, vaccinia infection and certain types of adenovirus infection. He agreed that the name superficial punctate keratitis no longer meant what it had in Fuchs' time and that it was appropriate to use it for the disease Thygeson had described.

In 1961 Thygeson[6] presented 29 additional cases and stated the five diagnostic features that he believed sufficient, in total, to differentiate the disease from all other types of the epithelial keratitis: (1) the chronic bilateral punctate epithelial nature of the keratitis, (2) the long duration with remissions and exacerbations, (3) the eventual healing without scars, (4) the lack of response to antibiotics, and (5) the striking symptomatic response to topical corticosteroids. At that time he believed that the superior limbal area was involved initially and in all exacerbations, but

not in the chronic phase of the disease, as distinguished from Braley and Alexander's[3] cases in which a filamentary keratitis in the upper third of the cornea accompanied the superior bulbar hyperemia.

Corneal sensation and tear function were normal, while visual acuity was reduced to 20/200 in only a few patients. None could remember an acute onset to their disease but they were aware of the day or week their symptoms had begun. The clinical course was as short as six months in one case, was four years in two cases, while the majority healed in two or three years. Topical corticosteroids were successful in treatment of all but one patient, a boy aged 13. Removal of the corneal epithelium was not successful because the keratitis recurred promptly in the newly formed epithelium. The youngest patient was a boy aged 6 and the oldest, a woman aged 68. Epidemiologic study showed no age or sex linkage, and there was no association with exposure of patients to persons similarly affected.

Bacterial cultures grew normal conjunctival flora, and conjunctival scraping yielded normal epithelium in ten cases and a few lymphocytes and monocytes in the remaining cases. Conjunctival scrapings from 11 patients were used for rabbit corneal inoculations, and material from 17 of the 29 patients was used for HeLa tissue culture inoculation; all were negative. While the dramatic effect of cortisone, comparable in its effectiveness to the treatment of phlyctenulosis, might suggest an allergic cause for the keratitis, Thygeson[6] believed the disease probably was caused by a virus because of (1) the absence of other infectious agents, (2) the occasional finding of mononuclear cells in conjunctival scrapings, and (3) the morphology of the corneal lesions that resembled measles and adenovirus infections.

Jones[7] was the first to suggest in 1963 that superficial punctate keratitis should formally be called Thygeson's Superficial Punctate Keratitis, an eponym honoring Dr Thygeson for his contributions to the field. Jones presented 27 cases; the youngest patient was 9 and the oldest was 53 years of age. While several patients had been able to stop treatment after only two years, the case of the longest duration was 11 years. The corneal lesions were circular, oval, or elongated, occasionally with a ragged edge or stellate appearance (the latter less regular than those of herpetic epithelial keratitis). Each opacity was composed of a collection of white dots, with the surface raised above the rest of the corneal surface. Jones[7] pointed out that Thygeson[1,6,8] had mentioned only epithelial lesions without a subepithelial component while Braley[2] and Braley and Alexander[3] had referred to both epithelial and subepithelial lesions. Jones[7] believed that the lesions were almost entirely epithelial but that there

was in addition a faint opacification of the superficial stroma underlying the epithelial opacity. This stromal opacity had the gray appearance of lamellar separation caused by edema rather than the hard or fine dot-like appearance of cellular infiltration. When viewed by retroillumination the stromal disturbance was found to be transparent, with the opacity residing entirely in the epithelium. This was in contrast to adenovirus keratitis in which the subepithelial component was an infiltration rather than edema alone. Jones was unsuccessful in four attempts to isolate a virus from corneal scrapings taken from four of his cases and placed into HeLa tissue culture. He commented that the previously reported isolation of a virus by Braley had not been accompanied by controls and that the procedure used in this isolation of intracerebral inoculation of mouse brain was known to unmask latent mouse viruses.

Jones[7] confirmed the benefit of corticosteroids that suppressed both signs and symptoms in 25 of his 27 cases. He tested the new drug, idoxuridine, in one eye of three bilaterally affected patients in a double-blind study, but found the drug without effect. He described the condition as a chronic, bilateral remittent corneal disease, with punctate epithelial keratitis occurring in the absence of conjunctivitis apart from some superior bulbar inflammation. In the absence of any evidence of communicable disease or direct evidence of a virus, he suggested that the disease might be a dyskeratosis rather than an infection.

In 1966 Thygeson[8] presented 27 unreported cases of TSPK, all of which shared an insidious onset, a prolonged course with exacerbations and remissions, slightly raised corneal opacities (each composed of numerous grayish granular dots), and minimal conjunctival hyperemia characteristic of the disease. There was no hyperemia of the superior limbal conjunctiva that he had previously believed to be part of TSPK,[1,6] but now considered a separate disease.[8] The youngest patient was 6 and the oldest 62 years of age; most cases resolved after three years, although one was still active after four years. Thygeson[8] believed a viral etiology was suggested by the absence of bacteria or other microorganisms, by resistance of the disease to sulfonamides and antibiotics, by the scanty mononuclear exudate, and by the viral type of epithelial lesions displaying a startling resemblance to the keratitis of measles. However, of the 14 cases subjected to virologic study, none yielded a viral agent on culture. In contrast to Jones'[7] report of the lack of effect of topical idoxuridine, Thygeson[8] found this drug produced subepithelial ghost opacities larger than the epithelial lesions. When the drug was discontinued and corticosteroids begun, the epithelial lesions could be suppressed but the subepithelial opacities persisted.

Thygeson expressed caution about the use of idoxuridine and also warned that corticosteroids, although effective, should be employed with care.

In France, Brini and Payeur[11] reported two cases, and Quéré et al,[12] two more along with 14 cases he had treated in Dakar, Africa. In a more extensive paper in 1968, Quéré et al[13] added two additional cases and discussed the cause of TSPK in detail. They believed the disease had three stages: a stage of onset lasting one to two weeks, a developmental stage up to eight months, and a stage of regression of several months to three years. In the stage of onset there was catarrhal inflammation, photophobia, and tearing; during the developmental phase the signs of conjunctival inflammation nearly disappeared, leaving the corneal epithelial lesions; and during the regressive phase the lesions became fewer in number and smaller in size until they finally vanished. While a viral cause continued to be most reasonable because of the morphology of the corneal lesions, the failure to isolate a virus led them to propose an allergic theory as the cause of TSPK. They pointed out the extraordinary effect of corticosteroids, the lability of the lesions, and the similarity of the corneal lesions to "urticaria of the cornea." Five years later Quéré et al[14] presented 11 additional cases in which the duration of the corneal disease was longer than they had initially thought, and suggested that the disease could become chronic.

From Japan in 1971, Wakui et al[15] described the clinical and electron microscopic characteristics of several corneal diseases including TSPK. The duration of corneal disease in one of their patients with TSPK was 16 years, with no evidence of remission, which they pointed out was in contrast to the much shorter duration found by Thygeson[8] in his most recent paper. Electron microscopy of the corneal epithelium taken from affected patients failed to reveal virus particles but did show cell destruction confined to one discrete area, in contrast to the cell-to-cell spread of destruction observed in herpes simplex keratitis.

The first successful isolation of a virus by tissue culture was reported by Lemp et al[16] in 1974. A 10-year-old white boy who had had varicella at age 4, and had not recently been exposed to viral exanthems, developed 15 to 20 discrete grouped punctate epithelial lesions characteristic of TSPK on both corneas. A moistened cotton-tipped swab was rubbed over the unanesthetized corneal surface and placed in tissue culture medium, which was then used to inoculate HEP-2 cells. Positive cytopathology was observed in this cell line, and passage was successfully made to WI-38 tissue culture. A plaque reduction test was positive for varicella zoster virus, and DNA inhibitors prevented viral multiplication. Lemp et al pointed out that remissions and exacerbations of disease are characteristic

of latent viral infections, especially in the herpes group of viruses, including varicella zoster virus. The remissions and exacerbations of TSPK might represent sporadic spread of varicella zoster virus from deeper sensory ganglia to the cornea, while the persistence of the epithelial lesions might be a hypersensitivity. Support for the role of varicella zoster virus was provided by Dawson who, in a personal communication, reported to Lemp et al[16] that he had found virus-like particles of a size consistent with varicella zoster virus in the corneal epithelium of a patient with TSPK.

Sundmacher et al[17] were the first to report the beneficial effect of hydrophilic soft contact lenses in the treatment of TSPK. Three of his ten patients obtained symptomatic relief from these lenses, although the lenses did not alter the corneal pathology. In addition, human leukocyte interferon used topically for several weeks did not affect the course of the disease in two patients. From seven of the ten patients, viral cultures were taken by removing individual corneal epithelial lesions with a blade and placing them in human diploid fibroblast tissue culture. Even after several passages, no virus could be isolated. Electron microscopic examination of diseased corneal epithelial cells from these seven cases failed to reveal viral particles, but necrosis and round cell infiltration were found. The fourth case illustrates the perils of confusing TSPK with herpes keratitis. A 24-year-old man who had corneal disease for four years was treated with antiviral agents, corneal debridment, iodine scrub, three applications of cryotherapy and one of heat therapy. Because of the previous treatments there was permanent corneal scarring, but the use of corticosteroids greatly benefited him after the correct diagnosis had been made.

To explain the ineffectiveness of interferon and the failure to identify the virus by electron microscopy, Sundmacher et al[17] suggested that the virus being sought could be in a latent form within epithelial cells. The altered genetic identity of the cell would stimulate the immune system and cause lymphocytes to surround the affected cells in a hypersensitivity reaction, sensitive clinically to topical corticosteroids.

Two additional cases of TSPK were added to the literature in 1978 in a brief report[18] that strongly recommended topical corticosteroid therapy. In the following year, Forstot and Binder[19] confirmed the beneficial effect of bandage soft contact lenses for relieving symptoms of TSPK in three of their patients. Because the use of these lenses reduced or eliminated the need for corticosteroids, they recommended extended or daily wear soft contact lenses for the treatment of TSPK.

Persistent subepithelial infiltrates at the site of healed epithelial lesions were reported by Abbott and Forster[9] in 1979 in a case of TSPK associated with Salzmann's nodular degeneration. This case was unusual because infiltrates without epithelial lesions were thought to occur only following application of topical idoxuridine, but this patient had never received antiviral therapy. They believed the 16-year duration of the case was longer than others reported, but a case of similar duration had been described by Wakui et al[15] in the Japanese literature.

Therapeutic soft contact lenses were recommended in 1980 by Goldberg et al,[10] who described success in relieving symptoms in four patients. In the first patient, lenses led to a resolution of epithelial lesions but subepithelial opacities persisted. Similarly, in the fourth patient, lenses reduced the number of epithelial lesions but did not affect two peripheral corneal lesions with subepithelial scarring. Of interest was the second patient, a physician who had controlled his TSPK for 16 years with topical corticosteroids; he was able to dispense with topical therapy within days of being fitted with soft contact lenses.

At the American Academy of Ophthalmology meeting in 1980, Tabbara et al[20] described 45 new cases seen at The Proctor Foundation. The mean age of 29 ranged from 2.5 years to 70 years; there were 28 men and 17 women. Ninety-six percent were affected bilaterally, and there was no association with systemic infection or conjunctivitis. The duration of the disease was from one month to 24 years, with an average of 3½ years. The authors made a distinction between the appearance of active lesions which were oval or round and composed of fine intraepithelial lesions appearing in the visual axis, and inactive lesions, which were flat, intraepithelial gray dots that did not take stain. Subepithelial opacities were seen in 44% (20) of the patients but of this group 80% (16) had previously been treated with topical idoxuridine.

The authors believed that subepithelial opacities were specifically related to antiviral therapy and were not characteristic of TSPK. Visual acuity in two patients was reduced to 20/100, in three patients to 20/80, in eight patients to 20/50, and in 32 patients to 20/30. Although ten viral cultures were negative, the authors believed a viral cause was suggested by the morphology of the corneal lesions (similar to that of measles), by the protracted course, and by the mononuclear cell infiltrate. In their opinion, topical corticosteroids relieved symptoms but prolonged the course of the disease; they recommended contact lens fitting, which they found successful in two patients. In a comment to the presentation,[20] O'Day questioned whether corticosteroids prolonged the course of the disease.

METHODS

Thirty-six unreported cases of TSPK are the subject of this thesis. All patients—private and clinic—were examined by staff members of the Cornea Clinic or External Disease Clinic (College of Physicians and Surgeons, New York City), who confirmed the diagnosis of TSPK.

LABORATORY TESTS

Virus Cultures

Topical proparacaine hydrochloride was used to anesthetize the inferior tarsal conjunctiva, which was then rubbed with a moistened cotton-tip applicator. The applicator was placed in transport medium and the latter inoculated within two hours by Virology Laboratory personnel into WI-38, embryonic African green monkey kidney, and human embryonic kidney tissue cultures. These cultures were passed twice and observed for evidence of cytopathology.

Bacterial Cultures

Material from both the lid margins and the inferior tarsal conjunctiva was obtained after topical proparacaine hydrochloride anesthesia by rubbing the appropriate areas with moistened cotton-tip applicators, which were then inoculated into blood agar, chocolate agar, and EMB agar plates. These were incubated in the usual manner and growth confirmed by the Ocular Microbiology Laboratory.

Cytology

Material for cytologic examination was taken from the anesthetized inferior tarsal conjunctiva and superior tarsal conjunctiva with a sterile platinum spatula. The material was placed on a glass slide and examined with Giemsa stain.

Histocompatibility Typing

Peripheral blood lymphocytes were typed for 16 HLA A, 18 HLA B, and five HLA C antigens, using the standard microlymphocytotoxicity technique of Mital et al,[21] by the Immunogenetics Laboratory. B cell enriched lymphocyte suspensions were typed for eight HLA DR antigens, using the two-color fluorescence method of van Rood et al,[22] by the Immunogenetics Laboratory.

RESULTS

CHARACTERISTICS OF THE PATIENT GROUP

The age of onset of clinical symptoms ranged from 2.9 to 54 years of age, with an average of 27.6 years and a median of 25 years (Fig 1). In most

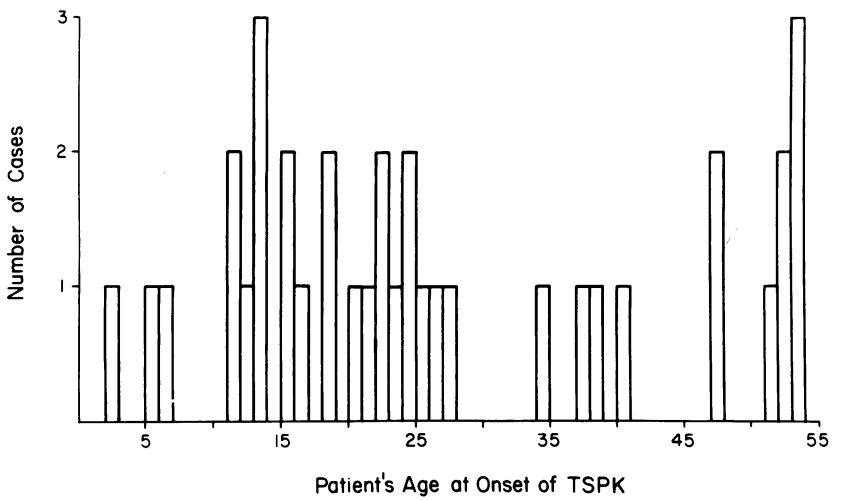

FIGURE 1
Histogram comparing age of patient in years at onset of TSPK with number of cases in each age grouping.

cases there was a delay between the onset of symptoms and the diagnosis of TSPK. This delay ranged between zero and six years, with an average of 4.6 years and a median of two years. The disease was bilateral in 93% (33) of cases; there were 29 women and seven men. In all but two cases there was no association with systemic illness, but in one case there was conjunctivitis for three days at onset and in the other case each recurrence was associated with symptoms of upper respiratory infection and systemic lymphocytosis. Total duration of the disease ranged from 0.3 to 30 years, with an average of 7.5 and a median of four years (Fig 2). Symptoms of tearing, irritation, photophobia, and variable difficulty with vision were reported by most patients at some stage of their disease. During the acute stage of keratitis, visual acuity was reduced to 20/200 in one patient, 20/60 in two patients, 20/50 in two patients, 20/40 in four

patients, 20/30 in ten patients, while 17 patients maintained 20/20.

In 25 of the 36 cases, classic oval grouped epithelial keratitis was observed while in 11 cases smaller punctate lesions or branched lesions were present. In 21 patients, subepithelial opacities were seen that were unassociated with overlying epithelial staining lesions in five patients. Topical corticosteroids provided dramatic improvement in both symptoms and physical signs in 35 patients to whom they were given. Two patients fitted with soft contact lenses and one patient fitted with hard contact lenses became symptom-free.

Thirty-one virus cultures taken from the inferior tarsal conjunctiva of 24 patients, several tested on more than one occasion, were all reported negative for virus. Bacterial cultures taken from the inferior tarsal conjunctiva of 20 patients revealed preponderantly *Staphylococcus epidermidis*, with no significant ocular pathogens. Cytologic examination of Giemsa-stained conjunctival smears from 19 patients revealed scanty inflammatory exudate with a preponderance of lymphocytes. Material from corneal scrapings from two patients was examined by electron microscopy, but no viral structures were identified according to T. Iwamoto, MD (oral communication, May 1980).

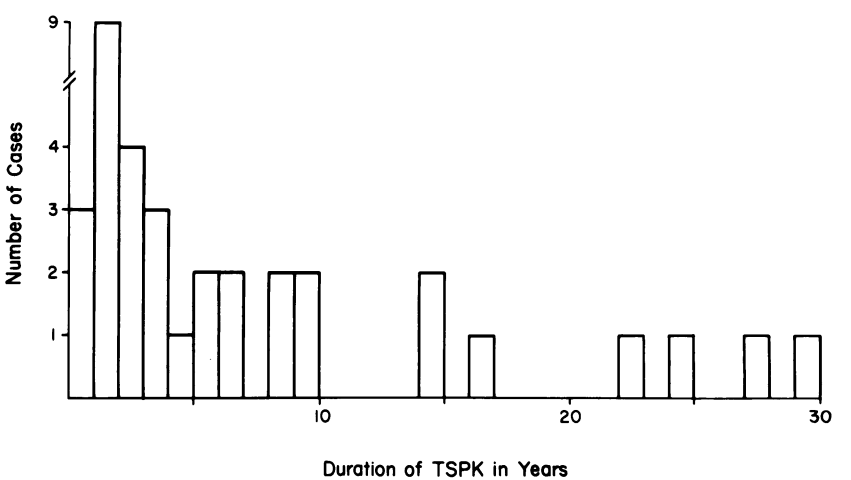

FIGURE 2
Histogram comparing total duration of each case of TSPK in years with number of cases in each group.

TABLE: RELATIVE RISK OF TSPK FOR PERSONS WITH ANTIGENS DR1- THROUGH DR8

ANTIGEN HLA	CONTROLS NO.	CONTROLS ANTIGEN FREQUENCY (N = 133)	CONTROLS GENE FREQUENCY (N = 266)	TSPK NO.	TSPK ANTIGEN FREQUENCY (N = 20)	TSPK GENE FREQUENCY (N = 40)	RELATIVE RISK	FISHER P
DR1	20	0.150	0.078	5	0.250	0.134	1.88	0.206E 00
DR2	33	0.248	0.133	6	0.300	0.163	1.30	0.400E 00
DR3	20	0.150	0.078	10	0.500	0.293	5.65	0.961E-03
DR4	44	0.331	0.182	2	0.100	0.051	0.22	0.266E-01
DR5	29	0.218	0.116	6	0.300	0.163	1.54	0.290E 00
DR6	25	0.188	0.099	2	0.100	0.051	0.48	0.270E 00
DR7	34	0.256	0.137	4	0.200	0.106	0.73	0.411E 00
DR8	11	0.083	0.042	1	0.050	0.025	0.58	0.516E 00

HISTOCOMPATIBILITY ANTIGENS

The frequency of HLA A, HLA B, and HLA C antigens in patients did not differ from that observed in 133 unrelated healthy Caucasoids, who were typed in parallel as controls. The Table shows the results when the relative risk of TSPK was analyzed for various HLA DR antigens. There was a significant increase in the antigen frequency of DR3, the relative risk being 5.65 ($P < .001$). The relative risk is defined as the product of the number of patients with the antigen and the number of controls without the antigen divided by the product of the number of patients without the antigen and the number of controls with the antigen.

DISCUSSION

CHARACTERISTICS OF THE CORNEAL SIGNS

The classic corneal sign of TSPK is a grouped punctate epithelial keratitis in an oval shape, staining with fluorescein, somewhat raised above the

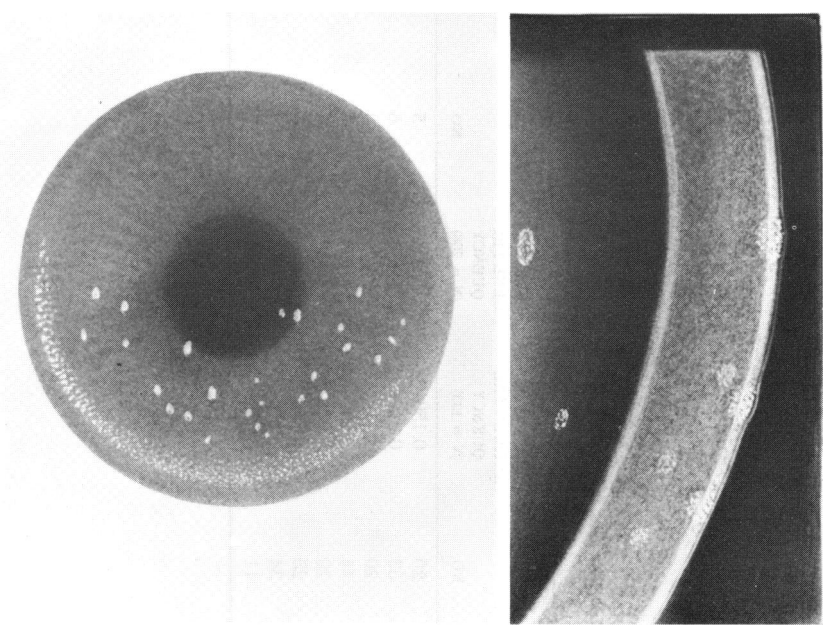

FIGURE 3
Artist's drawing of slit-lamp appearance of left eye (case 1) in 1963, depicting 26 epithelial lesions in vertically oval shape, elevating surface of corneal epithelium and not associated with subepithelial infiltration.

corneal surface, located in the pupillary axis but not accompanied by subepithelial infiltration.[6-8] However, this classic sign may not be observed in some patients who have an appropriate long history of recurrent corneal epithelial disease and keratitis sensitive to topical corticosteroids. Such a case could be considered to be atypical TSPK until such time as the classic epithelial lesions are observed. The oval, grouped punctate epithelial keratitis is present during active phases of the disease. During inactive stages the lesions can be flat gray intraepithelial dots that do not stain, or they may present a stellate appearance that can be confused with herpes simplex keratitis.[13,20] Topical corticosteroids can alter the epithelial lesions and antiviral agents may increase the degree of subepithelial infiltration.[8,20] The variation in corneal signs is well demonstrated by case 1, which has been followed for 27 years and recorded by drawings or slit-lamp photographs for the past 17 years.

CASE REPORTS

CASE 1

In January 1954 a 53-year-old baker developed burning and redness of his left eye that was caused by punctate keratitis lasting for several months. Two years later the right eye became affected and there was recurrence of the disease in his left eye, both of which responded to silver nitrate scrub of the tarsal conjunctiva. In 1963 the Cornea Clinic noted bilateral grouped epithelial keratitis, and a drawing of the left cornea was made (Fig 3). The artist depicted 26 epithelial lesions, each in a vertically oval shape, which elevated the surface of the corneal epithelium and was not associated with subepithelial infiltration. Topical corticosteroids administered in the left eye yielded marked improvement in signs and symptoms, while topical idoxuridine drops given every hour to the right eye were associated with an increase in subepithelial opacities and no improvement in the epithelial lesions. Recurrent attacks during the succeeding two years were treated with topical corticosteroids but it was not until 1967 that the diagnosis of TSPK was established. For therapeutic reasons the epithelium was removed from the right cornea, which provided an improvement in symptoms for six weeks, after which the disease recurred. Material from the corneal scraping was prepared for both a virus culture (subsequently reported negative) and for electron microscopy, which showed degenerative changes in the corneal epithelium without evidence of virus particles. During an inactive phase of the disease in 1968, a slit-lamp photograph of the left cornea showed six small, round, punctate epithelial lesions that are consistent with TSPK but not the classic lesions of active disease (Fig 4).

A severe recurrence in 1969 reduced visual acuity to 20/40 OD, 20/80 OS—the worst obtained during the course of the patient's disease. A slit-lamp photograph of the left eye showed an excess of 30 epithelial lesions, some associated with subepithelial opacities (Fig 5). At the superior edge of the direct slit-lamp beam

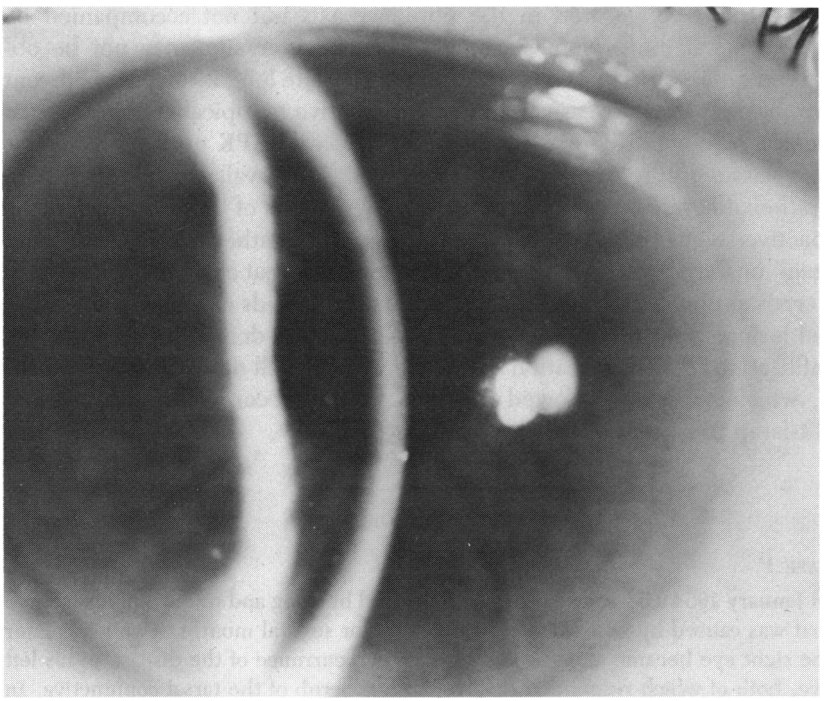

FIGURE 4
Slit-lamp photograph of left eye (case 1) in 1968, showing six small, round punctate epithelial lesions found during inactive phases of disease.

the grouped nature of the oval punctate epithelial keratitis can be seen. One year later, during a remission, visual acuity returned to 20/20 and a slit-lamp photograph of the left cornea shows the small size and round shape of epithelial lesions during a less active phase of corneal disease (Fig 6). During a recurrence in 1977, a slit-lamp photograph of the left cornea revealed in the direct slit-lamp beam two classic oval-shaped, grouped epithelial punctate keratitis lesions and, by retroillumination, four oval epithelial lesions (Fig 7).

In 1980 a slit-lamp photograph of the left cornea, stained with fluorescein and illuminated by cobalt blue filter, showed the stellate and pseudodendritic appearance of atypical epithelial lesion in TSPK (Fig 8). These can be confused with herpes simplex keratitis and inappropriately treated. From 1954 to 1981 this patient has been followed both in private officies and in the Cornea Clinic for a total of 63 office visits. He has not developed permanent subepithelial opacities in the absence of epithelial disease and is well controlled on extremely low doses of

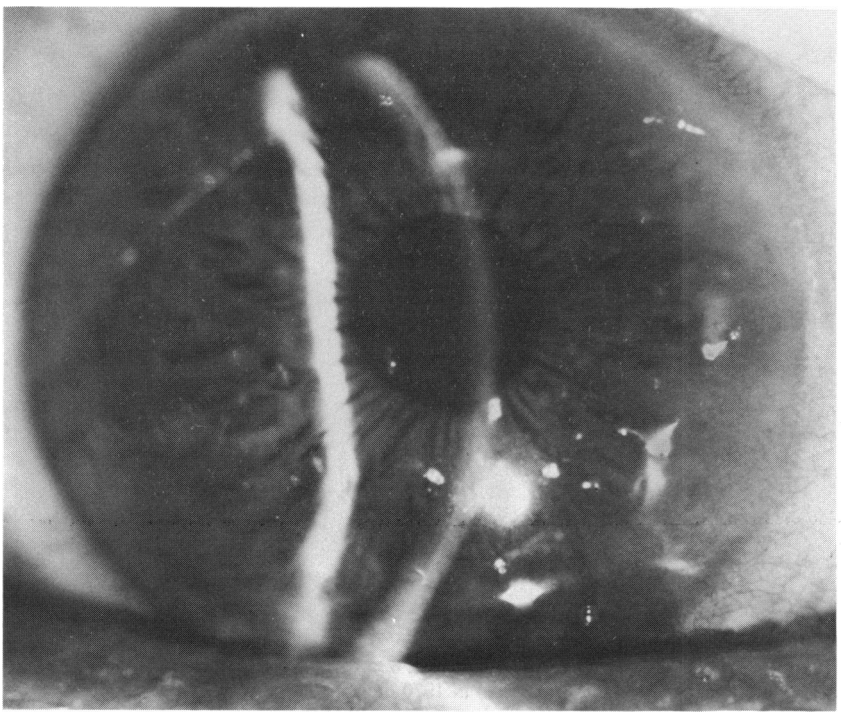

FIGURE 5
Slit-lamp photograph of left eye (case 1) in 1969 during severe recurrence of keratitis, showing more than 30 epithelial lesions associated with subepithelial opacities. Punctate epithelial lesion at superior edge of direct slit-lamp beam demonstrates grouped nature of classic lesions. Filamentary type of lesion is seen in pupillary area.

topical corticosteroids. There have been no complications with cataract or glaucoma secondary to the prolonged use of corticosteroids.

This case illustrates the variations in the corneal signs of TSPK over time. If the classic grouped epithelial punctate keratitis is not found on first examination, a diagnosis of TSPK still can be considered on the basis of atypical epithelial signs supported by a history of recurrent keratitis, absence of other causes of corneal disease, and response to topical corticosteroids. It is most important to rule out herpes simplex keratitis because, while it benefits from topical idoxuridine and is aggravated by topical corticosteroids, the exact opposite is true of TSPK, which is worsened by topical idoxuridine and improved by corticosteroids. This differential may

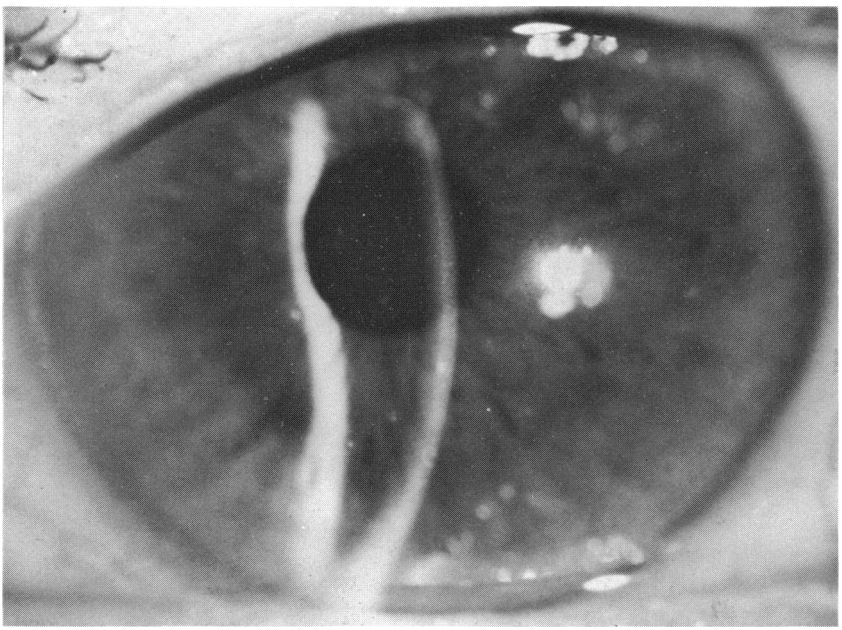

FIGURE 6
Slit-lamp photograph of left eye (case 1) in 1970 during remission, showing small size and round shape of less active epithelial lesions.

be difficult when a few pseudodendritic corneal lesions are the initial sign.

There is a controvesy in the literature concerning the association of subepithelial opacities with TSPK. The original description of the disease by Thygeson[1] referred to an intraepithelial opacity with little if any subepithelial edema and no subepithelial infiltrates. However, Braley[2] and Braley and Alexander[3] described the disease as a bilateral keratitis characterized by epithelial and subepithelial opacities. Sigiura et al[4] believed that the opacities were limited to the epithelium and usually did not penetrate into the stroma unless there was severe inflammation. Opacities associated with severe epithelial lesions could extend to one fifth of the stromal layer.

Thygeson[6] in 1961, restated his belief that each opacity was strictly epithelial, a view supported in 1963 by Jones,[7] who stated that in spite of recurrent epithelial lesions the stroma never became more than trivially or slightly involved. The faint opacification of the superficial stroma un-

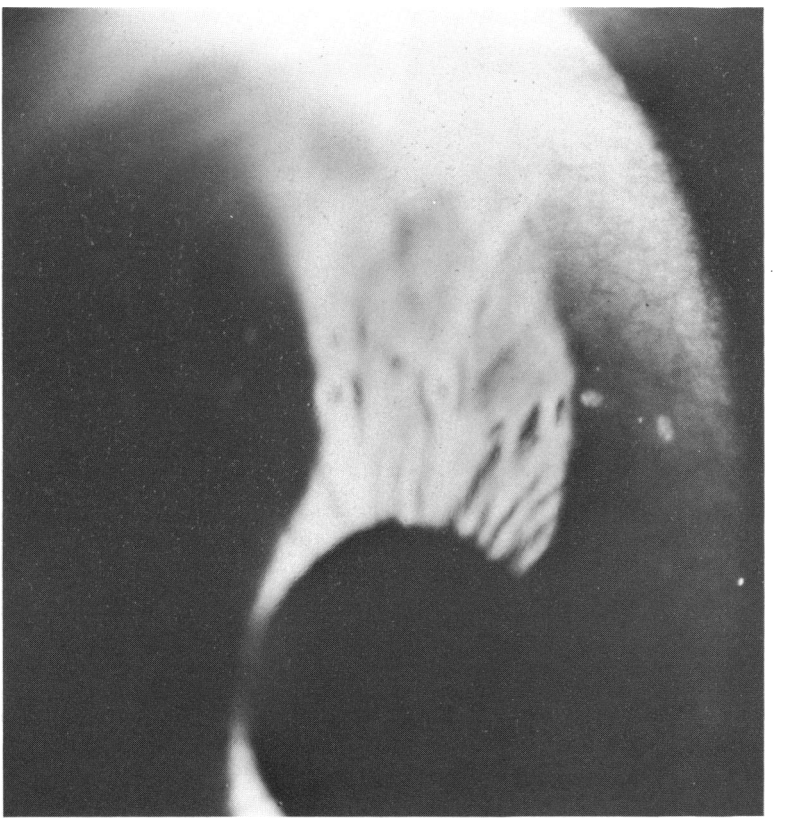

FIGURE 7
Slit-lamp photograph of left eye (case 1) in 1977, showing in direct slit-lamp beam two classic oval, grouped epithelial lesions and by retroillumination, four oval epithelial lesions.

derlying the epithelial keratitis had a stippled gray appearance of lamellar separation from slight edema rather than the hard, fine discrete dots of cellular infiltration. While there were combined epithelial and subepithelial opacities somewhat like those occurring with adenovirus and other viral infections, there was an important difference. This difference could be resolved by retroillumination of the stromal disturbance of TSPK. The stromal component of TSPK is transparent and all the opacity resides in the epithelial lesion, in contrast to the stromal disturbance associated with adenovirus and other viral diseases in which retroillumination reveals that the opacity is in the subepithelial component.

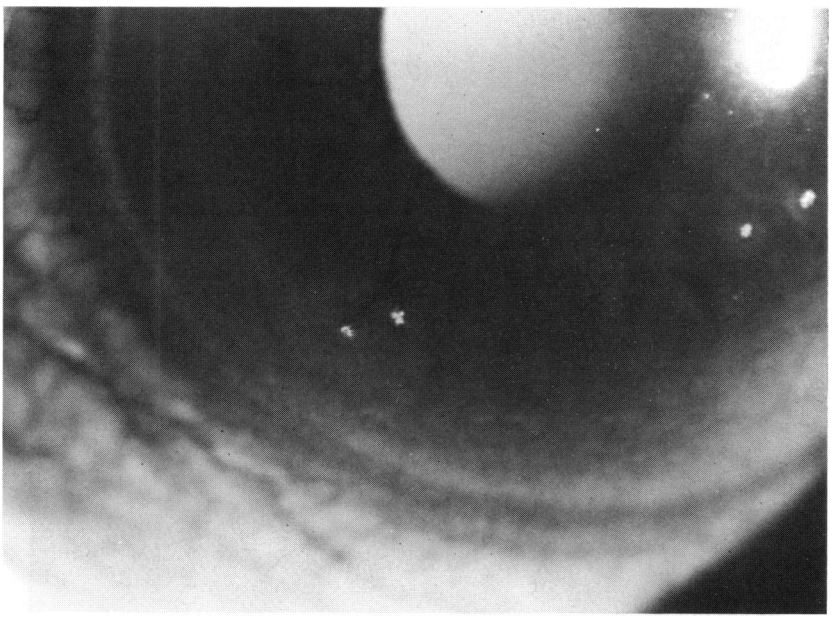

FIGURE 8
Slit-lamp photograph of left eye (case 1) in 1980, showing branched or pseudodendritic appearance of atypical corneal lesions. Photograph was taken with cobalt blue light after staining corneal lesions with fluorescein.

In 1966 Thygeson[8] restated his belief that the lesions of TSPK were strictly epithelial. However, in all four patients treated with topical idoxuridine, subepithelial ghost opacities appeared directly beneath the epithelial lesions and these ghost opacities were larger than the epithelial component. When idoxuridine was discontinued and corticosteroids started, the epithelial lesions could be suppressed but the subepithelial lesions persisted. Thus, Thygeson[8] believed the persistent subepithelial component was related not to the natural history of TSPK but to the use of topical antiviral agents. The epithelial nature of the lesions was supported by Quéré et al,[12-14] who referred to strictly intraepithelial signs that might reach down to Bowman's membrane during an active phase, and by Wakui et al,[15] who described the corneal disease as superficial corneal opacities alone.

Lemp et al[16] described the corneal signs of TSPK as discrete whitish infiltrates occurring within the epithelium and the immediately under-

lying structures and believed that similar but not identical lesions could be seen in epidemic keratoconjunctivitis, trachoma, variola, herpes simplex, vaccinia, and rosacea. Sundmacher et al[17] reported epithelial lesions without corneal scarring but with a trace of stromal edema. The three patients of Forstot and Binder[19] also had lesions that were strictly epithelial.

This view was disputed by Abbott and Forster,[9] who reported a case followed for 14 years that developed both subepithelial scarring and gray nodules resembling Salzmann's degeneration. On first examination in 1964 opacities were observed in both epithelium and Bowman's membrane. In 1971 and 1978 numerous subepithelial scars and several active epithelial lesions of TSPK were observed. Since this patient had never been treated with topical idoxuridine, yet had developed permanent subepithelial opacities, these opacities appeared to be part of the natural history of the disease. Of 45 new cases reported by Tabbara et al,[20] 44% (20) had subepithelial opacities. However, they did not believe subepithelial opacities were part of the natural history of the disease and attributed their appearance to the fact that 80% of patients with subepithelial opacities had previously been treated with idoxuridine.

Goldberg et al[10] found subepithelial opacities in their first and fourth case. Their first patient had resolution of epithelial opacities with the use of an extended wear contact lens, but subepithelial opacities persisted. The fourth patient had an 11-year-history of TSPK originally diagnosed by Thygeson. In addition to typical epithelial lesions there were two peripheral lesions that had obvious scarring. The authors believed that prolonged duration of the disease appeared to have the potential for producing subepithelial corneal scarring.

Among the 36 patients in the present study, 50% (18) had subepithelial infiltrates and 41% (15) had received topical antiviral therapy. However, of those patients given antiviral agents, only 40% (14) developed subepithelial opacities. This evidence supports the belief that subepithelial opacities are part of the natural history of TSPK and not the result of treatment with topical antiviral agents. More than a fine diagnostic point is involved in determining whether subepithelial opacities can be a part of the TSPK complex. If the corneal lesions are strictly limited to the epithelium and associated only with anterior stromal edema and not with infiltration or opacity, then the corneal disease is unlike that of adenovirus, herpes simplex virus, variola virus, and varicella zoster virus keratitis. If, on the other hand, the corneal disease of TSPK does include subepithelial opacities and infiltrates, the corneal signs more closely resemble the keratitis produced by these viruses.

THEORY OF VIRAL ETIOLOGY

Thygeson[8] pointed out in 1966 that the viral etiology of TSPK was strongly suggested by (1) the absence of bacteria or other microorganisms, (2) the resistance of the disease to sulfonamides and antibiotics, (3) the scanty mononuclear cell exudate on conjunctival scrapings, and (4) the viral type of the epithelial lesions. In addition, he noted the startling resemblance between the keratitis of TSPK and the keratitis of variola, an association that favored the concept that TSPK was caused by a virus. While a virus was not isolated from the conjunctiva of any patient in the present study, one patient offered the opportunity to test both acute and convalescent blood serum for the presence of a rise in antibody titers against several viruses.

CASE 2

A 35-year-old female nurse developed irritation, blurring, and photophobia in her right eye and sought ophthalmic examination the following day. Two staining epithelial lesions on the right cornea were thought to be herpes simplex keratitis, and topical antiviral agents were prescribed.

On the 11th day after onset the patient was examined in consultation, and several classic grouped epithelial punctate lesions were seen on the right cornea, without any subepithelial opacities or conjunctival reaction. Blood was drawn for HLA studies and for acute serum antibody determinations. The patient's signs and symptoms improved after the use of topical corticosteroids. By the 17th day the corneal lesions had cleared, and topical corticosteroids were discontinued. On both the 17th and the 24th day blood was drawn for convalescent serum antibody determinations. The corneal signs and symptoms recurred on the 30th day with return of three grouped epithelial lesions on the right cornea that responded to topical corticosteroids. Since that time the patient has had several recurrences of TSPK.

The serum taken on the 11th, 17th, and 24th days following onset was tested for a rise in antibody titer against adenovirus, varicella zoster virus, herpes simplex virus, mumps virus, and variola virus but none was found. The absence of a rise in antibody titer can be explained by assuming that a virus other than those tested is responsible for the disease or that the severity of the local ocular infection was insufficient to stimulate a systemic antibody response.

HERPES VIRUS GROUP (VARICELLA ZOSTER AND HERPES SIMPLEX)

In 1974 Lemp et al[16] isolated varicella zoster virus from the cornea of an 11-year-old boy with bilateral TSPK who had had varicella infection in childhood but no recent systemic infection. In spite of many attempts by

other authors to isolate a virus in tissue culture, no success has been reported. The isolation reported by Braley[2] and Braley and Alexander[3] has been challenged because the method employed intracerebral inoculation of mice, which can unmask latent mouse viruses.[7] Support for the conclusion by Lemp et al[16] that varicella zoster virus might be responsible for TSPK came from a personal communication to him by Dawson,[16] who said he had found viral particles of appropriate size and shape to be consistent with varicella zoster virus as determined by electron microscopy of corneal epithelium from TSPK patients. Neither Wakui et al[15] nor Sundmacher et al[17] could identify virus particles by electron microscopy in corneal epithelium from TSPK patients, but Sundmacher et al[17] did note the presence of lymphocytes adjacent to affected epithelial cells. Corneal epithelium from two patients in the present study was examined by electron microscopy but no virus particles were found.

Nearly all patients in the present study gave a history of chicken pox, but there was one who could recall neither chicken pox nor shingles. In addition, one case is of great interest because the onset of TSPK preceded the development of chicken pox.

CASE 3

A 2-year 11-month-old boy was first examined by an ophthalmologist in May 1978 because of several weeks' history of burning and tearing in his right eye. While there was no conjunctival injection, multiple areas of corneal staining with underlying subepithelial opacities were observed. Because some of these staining areas were interpreted to have a dendritic pattern, herpes simplex virus infection was considered; however, because of the subepithelial opacities, adenovirus was also considered in the diagnosis. Topical adenine arabinoside was given but there was no improvement in the corneal signs until June 1978 when topical corticosteroids were added. There was marked improvement, and all topical medication was discontinued over the next few weeks. Five months after onset the boy developed a recurrence in his right eye in association with an upper respiratory infection. A virus culture was taken and subsequently reported to be negative. Seven months after onset both eyes became involved and, for this reason, consultation was requested.

Examination revealed only mild hyperemia and no preauricular nodes, but there were ten classic grouped punctate epithelial lesions on the right cornea and 12 on the left. Cytology was reported as scanty mononuclear exudate, and virus culture was subsequently reported as negative. The diagnosis of TSPK was made on the basis of the corneal signs and the history of recurrent keratitis responsive to topical corticosteroids.

Ten months after onset the boy developed acute chicken pox that was associated with a regression of his eye symptoms. However, one month after recovery from chicken pox there was a recurrence of the symptoms and slit-lamp examina-

tion revealed 20 classic epithelial lesions in each eye. A third virus culture taken at this time was also negative. On the last examination 2½ years after onset, typical grouped epithelial lesions were found on both corneas.

Varicella zoster virus infection in the nonimmune host, chicken pox, is a common childhood disease while the incidence of TSPK in all ages is much lower. However, in the immune host, the virus remains in the sensory ganglia, the source of retrograde spread to the skin or eye. Lemp et al[16] and Sundmacher et al[17] explored the concept that TSPK might be caused by the sporadic release of a virus from its former latent state, traveling down by the fifth nerve to produce corneal lesions. Varicella keratitis is characterized by dendrites with a gray-white raised epithelial lesion, fragmented configuration (sometimes without a terminal bulb), and poor-to-moderate fluorescein staining.[23] This is not the morphology of TSPK epithelial lesions. Varicella zoster virus was not the cause of TSPK in two patients in this study, the one with no history of chicken pox and the second in whom chicken pox developed long after the onset of TSPK.

Similarly, herpes simplex is latent in the dorsal root ganglion,[24,25] and pseudodendritic lesions are seen in TSPK, but herpes simplex is a relatively easy virus to isolate; if it were the cause of TSPK such isolation would have been accomplished. Furthermore, the corneal sensitivity is normal in TSPK but often reduced in herpetic keratitis.

ADENOVIRUS

Pharyngeoconjunctival fever (PCF) and epidemic keratoconjunctivitis (EKC) are the two clinical syndromes caused by the various adenovirus types.[26-29] PCF is a self-limited, acute follicular conjunctivitis with punctate or grouped epithelial keratitis and variable subepithelial infiltration of seven to 14 days' duration. On the other hand, EKC, runs a course of three weeks and is characterized by an initial week of acute follicular conjunctivitis, a second week of punctate epithelial keratitis, and a third week of subepithelial opacities and focal epithelial keratitis. These subepithelial opacities lessen with time and can be temporarily suppressed by topical corticosteroid therapy.

While PCF and EKC are self-limited diseases, there have been reports of adenovirus keratoconjunctivitis of long duration with recurrences and remissions.[30-33] Boniuk et al[30] reported a 59-year-old man followed for nearly two years because of recurrent keratitis of his left eye. Eight months after onset, and during a recurrence, adenovirus type 2 virus was isolated from a corneal scraping. Darougar et al[31] reported a case of

keratoconjunctivitis and recurrent papillary conjunctivitis lasting 16 months, from which adenovirus type 19 was isolated one year after onset. Pettit and Holland[32] found three cases of adenovirus infection with abnormally extended duration of disease. The first patient developed acute conjunctivitis with small- and medium- size subepithelial infiltrates in the right eye. During the next 16 months the infiltrates persisted, with overlying epithelial staining and remissions and exacerbations. Adenovirus type 3 was isolated from the right eye six months and 25 months after onset of the patient's symptoms. Their third patient had epithelial keratitis and subepithelial infiltrates in both eyes consistent with adenovirus infection. Viral cultures taken 13 weeks after onset of symptoms isolated adenovirus type 5. Over the succeeding seven years the patient has had remissions and exacerbations of superficial punctate keratitis with subepithelial infiltration, and on last examination punctate epithelial keratitis in the absence of subepithelial opacities was observed.

Three cases in the present study present several similarities to chronic adenovirus infections although in all of them classic, grouped epithelial corneal lesions were observed at some point in the course of the disease.

CASE 4

In January 1971 a 7-year-old black girl developed cough and coryza and, two days later, diffuse punctate keratitis in the inferior nasal portion of the left cornea. Adenovirus infection was suspected, and the patient was treated with antibiotic drops. Three days later the right cornea was affected by punctate epithelial keratitis with small subepithelial infiltrates, but there was no evidence of conjunctival inflammation in either eye. One week after onset, because of the persistence of small subepithelial infiltrates, topical corticosteroids were used in both eyes for eight days.

Five weeks after onset, examination at the Cornea Clinic revealed several elevated and grouped epithelial lesions as well as fine punctate staining and scattered subepithelial infiltrates in both eyes. Because of the appearance of the corneal lesions and the relatively long course of the disease, the case was considered to be a variant of TSPK. Viral cultures were obtained but were reported negative.

Eighteen weeks after onset the patient woke up with painful red eyes, and slit-lamp examination revealed more than 20 epithelial staining areas in association with small subepithelial infiltrates in both corneas. Treatment with topical corticosteroids resulted in prompt improvement of both signs and symptoms. Twenty-one months after onset the Cornea Clinic found moderately large, slightly elevated, whitish grouped epithelial lesions associated with fine punctate staining in both corneas. There were no subepithelial opacities. In April 1977 three classic, grouped epithelial punctate lesions were seen on the left cornea

while the right cornea was clear. On last examination in May 1980 both corneas were uninvolved.

The history of cough and coryza in association with conjunctivitis, corneal staining, and subepithelial infiltrates is characteristic of adenovirus infection. However, no isolation of adenovirus could be made five weeks after onset, the clinical course was protracted to more than seven years with remissions and exacerbations, the subepithelial infiltrates were not permanent in location but changed their position, and classic, grouped punctate epithelial lesions were observed during the course of the disease.

CASE 5

In 1971, at age 19, a black woman developed pain, tearing, and photophobia in both eyes, which recurred several times before she was first examined in the Eye Clinic in 1974. Slit-lamp examination of both corneas revealed epithelial staining overlying subepithelial infiltrates. A virus culture was negative. Treatment with topical corticosteroids produced a dramatic improvement in symptoms, and the subepithelial infiltrates disappeared within seven days. On the basis of the long history of remissions and recurrences, the response to topical corticosteroids, and the appearance of the corneal lesions, a diagnosis of atypical TSPK was made. In April 1974 typical TSPK epithelial lesions were found in the left cornea, with faint subepithelial haze. These responded to topical corticosteroids. In October 1974 exacerbation associated with herpetic stomatitis was characterized by numerous punctate staining lesions in both corneas. During 1974 the patient had four clinic visits for recurrences of symptoms. In April 1977 examination in the External Disease Clinic revealed two classically grouped punctate epithelial lesions on the right cornea and seven on the left cornea. Cytologic examination revealed moderate lymphocytes in a scanty mononuclear cell exudate. Between August 1977 and March 1978 she was pregnant and reported a marked improvement in her eye symptoms. On her last visit in July 1980, slit-lamp examination revealed one classic grouped punctate epithelial lesion in the right cornea and 15 subepithelial small opacities without overlying epithelial staining, while in the left cornea there were ten small subepithelial opacities.

The prolonged course, remissions and exacerbations, response to topical corticosteroids, and finding of classic grouped epithelial punctate keratitis on several occasions supports the diagnosis of TSPK. However, the subepithelial opacities were particularly numerous and persistent and, in the absence of the other characteristics, might suggest adenovirus infection.

CASE 6

In March 1977 a 20½-year-old female ballet dancer developed irritation in both eyes and was told by an ophthalmologist that she had a virus infection. Six months later viral keratitis was diagnosed and topical idoxuridine prescribed. A corneal consultant noted that every time the patient had an episode of keratitis she would simultaneously develop a sore throat, fever, and systemic lymphocytosis. An elevated convalescent adenovirus titer was detected, but unfortunately there was no acute serum for comparison. Virus culture was negative.

The patient was first examined for this study in September 1980, and ten classic grouped punctate epithelial lesions were seen on the right cornea and 11 on the left. There were no subepithelial infiltrates. The patient declined to use topical corticosteroids, and on reexamination one month later 15 lesions were seen on the right cornea and 20 on the left; some had adopted a stellate pattern. Because her symptoms were not too severe the patient preferred not to use topical corticosteroids. A second virus culture was also reported as negative.

A diagnosis of adenovirus infection was made originally because of the association of the keratitis with sore throat, fever, and a relative lymphocytosis. However, the long duration of 3½ years, with remissions and exacerbations, is atypical for adenovirus infection. The classic morphology of the epithelial lesions observed in September 1980 was diagnostic for TSPK.

Adenovirus infections are not latent in the same sense that herpes simplex virus and varicella zoster virus can be latent in the sensory ganglia. However, there is evidence that adenovirus antigens persist in the anterior corneal stroma in a manner analogous to the persistence of herpes simplex virus in the anterior corneal stroma of chronically infected corneas.[28,34] Dawson et al[28] reported a patient with acute EKC who developed a recurrence of epithelial keratitis above the subepithelial infiltrates after the epithelium had been completely removed and allowed to grow back. The source of the new epithelial lesions was thought to be infectious elements from within the anterior stromal opacities.[28] Both TSPK and chronic adenovirus keratitis can develop grouped epithelial lesions, although in TSPK these lesions have a specific morphology of oval-shaped, grouped punctate epithelial keratitis. Subepithelial lesions are much more prominent in adenovirus keratitis but can be found in TSPK. There is usually a history of acute onset and a rise in serum antibody titers following adenovirus keratitis, but if the condition becomes chronic the antibody response is much less. It is significant that an adenovirus had been isolated from a case of TSPK.[35] The ability of some adenoviruses to persist over time and to recur must depend not only on the virulence of the virus but on the host's immune response.[29] Differ-

ences in the immune response may alter the course of a common viral infection of the cornea so that the same virus can produce different clinical syndromes in different persons.

ASSOCIATION OF TSPK WITH HISTOCOMPATIBILITY ANTIGENS

Research with highly inbred strains of mice has shown that the immune response genes are located within the major histocompatibility complex (MHC), the H2 system.[36-38] The functional homologue of the MHC in man is the HLA system, with the immune response genes mapping within the HLA D and HLA DR regions. To define the various antigens and molecules encoded by HLA genes both serologic and cellular methods have been employed. The HLA A, HLA B, and HLA C loci code for antigens that are present on the surface of essentially all nucleated cells of the body as well as on platelets. Typing for antigens coded by these three loci is done by complement mediated microcytotoxicity assay, specifically by incubating the lymphocytes from the person being tested with known antisera.[21,36] After incubation with complement the cells are tested by a dye exclusion technique to determine the presence of cytolysis, ie, of positive reactions, indicating the HLA A, HLA B, and HLA C phenotype of the cells.

On the other hand, HLA D antigens are limited in their distribution and are found on B but not on resting T lymphocytes.[36-38] The HLA D locus was defined by using cellular rather than serologic techniques. Lymphocytes from the person to be tested are grown in a mixed lymphocyte culture with homozygous typing cells (HTC) of all known HLA D specificities, and the phenotype of the responding lymphocytes is assigned on the basis of negative reactions to specific HTCs. More recently, serologic methods have been developed to detect antigens with limited tissue distribution that are related to the D region.[22] These serologically determined D-related antigens are called HLA DR antigens. It is believed that HLA D and HLA DR antigens are coded by very closely linked loci.[36-38] Thus the HLA D and HLA DR antigens are in strong linkage disequilibrium, and testing for HLA DR, which is less costly, can be substituted for HLA D testing.[36,38]

A number of diseases have been associated with an increased frequency of HLA Dw3 and HLA DR3 antigens. These are gluten-sensitive enteropathy, dermatitis herpetiformis, chronic hepatitis, Addison's disease, Sjögren's syndrome, Graves' disease, insulin-dependent diabetes mellitus, and systemic lupus erythematosis.[39-45] Analysis of patient statistics compared with controls, presented at a histocompatibility conference in 1980, provides the most recent information of the relative risk for a person

carrying HLA DR3 of developing four of these diseases. For chronic liver disease, including chronic active hepatitis, the relative risk is 2.2,[46] for myasthenia gravis 2.7,[47] for insulin-dependent diabetes mellitus 3.3,[48] and for coeliac disease 17.5.[49] The relative risk of a person with HLA DR3 developing TSPK in the present study is 5.65.

Diseases associated with HLA D and HLA DR often show a familial characteristic with incomplete or low penetrance, and women are more often affected.[50] Sometimes a clear dosage effect, with a tendency to recessivity,[50] can be observed. There is no known causal agent in HLA D- and HLA DR-associated diseases but a viral agent is strongly suggested, and there are numerous immunologic abnormalities of an autoimmune character.[50,51]

A number of possible mechanisms have been explored to explain the association between components of the HLA system and various diseases.[50-53]

1. The actual disease genes are not those coding specifically for the HLA antigens but are in close proximity to them on the short arm of chromosome 6. Alternatively, disease susceptibility may result from certain immune response genes that are in linkage disequilibrium with HLA D and HLA DR genes.

2. Molecular mimicry occurs when an infectious or other environmental agent has a similarity to a normal tissue antigen. This infectious or environmental agent will stimulate a weaker immune response than would occur if the agent were clearly different from normal tissue antigens.

3. The HLA type may determine cell surface receptors that facilitate the attachment of a virus to the cell and the ability of the cell to transport the virus across the cell membrane. This would increase the susceptibility of a person to a given viral infection.

4. The modified cell theory suggests that viruses could alter antigens coded for by the HLA D and DR region. These altered antigens would be regarded as foreign by the host and cause an autoimmune reaction.

TSPK may be caused by a common virus whose clinical effect on the corneal epithelium and stroma is determined by the presence of HLA DR3. Immune mechanisms are implied by the presence of lymphocytes in corneal lesions examined by electron microscopy, by the marked effect of topical corticosteroids, and by the chronic course of TSPK with remissions and exacerbations.

CONCLUSIONS

1. Thygeson's Superficial Punctate Keratitis (TSPK) is a chronic, primarily epithelial keratitis without acute symptomatic onset but with long

duration and many remissions and exacerbations. The classic oval grouped punctate epithelial lesions are seen during the active stages of the disease, while during the less active stages small, round epithelial lesions or pseudodendritic lesions occur. A significant number of patients develop subepithelial opacities that occasionally become permanent even in the absence of overlying epithelial disease. These subepithelial opacities are not specifically related to previous use of topical antiviral therapy but are part of the natural history of the disease.

2. Symptoms can be relieved and signs suppressed by using soft, extended wear, or hard contact lenses as well as by topical corticosteroids.

3. The concept that TSPK is caused by a virus is supported by the startling resemblence of the epithelial lesions of TSPK to those seen in variola and certain adenovirus infections, by electron microscopic evidence of virus particles in epithelial lesions, and by the isolation of both adenovirus and varicella zoster virus from eyes of patients with TSPK.

4. The frequency of histocompatability antigen HLA DR3 is significantly increased in patients with TSPK (Relative Risk = 5.6, $p < 0.001$). Because this antigen is associated with several autoimmune diseases, it is likely that immune mechanisms also play a role in TSPK. Further evidence for an immune mechanism is the lymphocytic response within corneal epithelial lesions and in conjunctival cytology, the dramatic response to topical corticosteroids, and the extended course of the disease."

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