DIABETIC CORNEAL NEUROPATHY*

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VARIOUS CORNEAL AND ANTERIOR SEGMENT ABNORMALITIES HAVE BEEN REPORTED to occur in patients with diabetes mellitus. The most significant reports describe: filamentous keratitis,[1] reduced corneal sensation,[2] neurotrophic corneal ulcers,[3] the presence of glucose in tears,[4] wrinkling of Descemet's membrane[5]; and a characteristic epithelial keratodystrophy observed in approximately one-third of diabetic patients.[6]

In 1979, a study by Neilson and Lund[7] showed significantly reduced corneal sensation, decreased vibratory perception, and associated areflexia among diabetic patients, compared to an age-related control group. There was clear correlation among these factors as well as correlation to age, duration of disease above 15 years, and correlation with the presence of diabetic retinopathy. These authors concluded that significant intercorrelations suggest that reduced corneal sensation forms part of the polyneuropathy seen in this disease.

In 1981 Schultz and co-authors[8] reported clinical observations in a group of randomly selected diabetic patients to determine whether specific and predictable corneal abnormalities exist in diabetes; and if so, to determine whether these changes correlate with other observed clinical and laboratory abnormalities. Conclusions from this study indicate that 47% to 64% of diabetic patients may show epithelial changes at any given time. Corneal lesions varied from superficial erosions (Fig 1) to extensive, full thickness, confluent epithelial defects (Fig 2); and occasional neuroparalytic keratopathy (Fig 3). The variation in prevalence of epithelial

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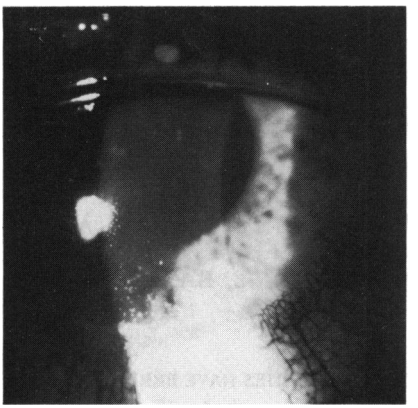

FIGURE 1
Punctate epithelial erosions of cornea present in diabetic patients with minimal corneal neuropathy.

defects (ie, 47% to 64%) was believed due to the transient nature of epithelial keratopathy seen in diabetes mellitus. These authors also found corneal sensation to be reduced in 18% of patients, decreased tear production was present in 47% of patients; *Staphylococcus epidermidis* was isolated from lid margins in 94% of patients; and preliminary information also suggested that reduced corneal sensation may be part of the peripheral neuropathy seen in diabetes.

In addition, electron microscopic studies of epithelial basement membrane failed to confirm structural defects that were specific for diabetic patients. Similarly, endothelial cell densities which were decreased in many patients were believed to be age-related and not specifically due to the presence of diabetes. The purpose of this paper is to analyze statisti-

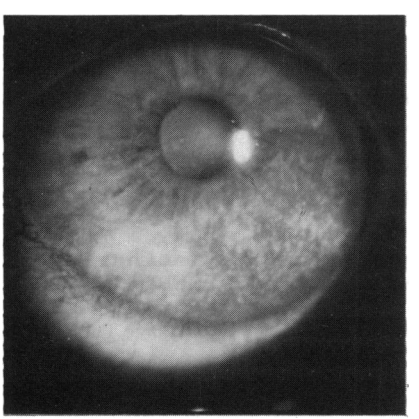

FIGURE 2
Moderate to severe (confluent) epithelial lesions observed in diabetic keratopathy.

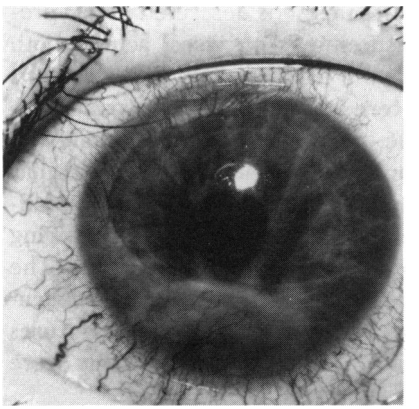

FIGURE 3
Occasional neuroparalytic keratopathy observed in patients with diabetes mellitus.

cally the clinical observations reported in this group of diabetic patients in an effort to characterize diabetic keratopathy and to determine whether specific correlations would indicate a probable pathogenesis of the corneal epithelial changes described in these patients.

METHODS

One hundred twenty diabetic patients were evaluated in the first year of the study. Ninety-eight patients were seen in the second year follow-up and 85 patients returned for the third year of examinations. Patients were lost to follow-up because of death, relocation, illness, and refusal to participate. Two patients entered the study in the second year. Patients were volunteers derived from the Metabolic Clinic of the Milwaukee County Medical Complex and not referred for ocular disease. A data base was created for each patient which included vital statistics, characterization of their diabetes, diabetic complications, past medical history, family history, occupational history, and ocular history including ocular complaints and ocular surgery.

Patients were subdivided into adult onset diabetes mellitus and juvenile onset diabetes mellitus recognizing that current nomenclature proposed by the National Diabetes Data Group[8] of the National Institutes of Health recommends classification related to insulin dependency. The designations "juvenile onset diabetes mellitus" and "adult onset diabetes mellitus" used in this study adhere to the recommended criteria established for type 1 (insulin-dependent) and type 2 (noninsulin-dependent) classifications.

Ophthalmologic evaluations utilized the methods described in our previous publication.[8] This included measurements of: visual acuity, both corrected and uncorrected; reflex and basic tear secretion by Schirmer's tests; semiquantitative tear glucose determinations with filter paper collection techniques; tear break-up time; corneal sensation utilizing the Luneau Coffignon anesthesiometer; corneal pachymetry; and intraocular pressure measurements. Slit-lamp observations noted: lid and conjunctival abnormalities, evaluation of corneal epithelium, and results following rose bengal and fluorescein staining of the conjunctiva and cornea. The iris and anterior chamber were also examined and gonioscopy and specular microscopy were performed on all eyes. Conjunctival and lid cultures were obtained as previously described.[8] The above evaluations were performed each year for all patients in the study.

Metabolic and neurologic evaluations included the following: fasting blood sugar values were obtained at the time of the eye examination in the first-year data set and hemoglobin Alc determinations were obtained in the second year of the study. The data base was expanded in the third year of the study to include: indirect ophthalmoscopy with fundus photography and vibration perception threshold measurements utilizing a Biothesiometer.[9] Vibration perception threshold was measured in both index fingers and both great toes and mean values for the upper and lower extremities were utilized in data analysis.

Patients were profiled metabolically during the third year examinations with collection of fasting urine and serum specimens. Measurements of reflex tear secretion as well as semiquantitative tear glucose measurement were made immediately following specimen collections. Patients were then given a 75 g oral glucose load and they were also given their normal insulin supplementation or oral hypoglycemic agent as indicated to approximate normal metabolic control conditions. Two hours later a second serum and urine collection was made. Simultaneous basic tear secretion and semiquantitative tear glucose measurements were then obtained. The following tests were performed on the serum samples: hemoglobin Alc determinations utilizing the method of Trivelli et al,[10] fasting blood sugar measurements using a glucose oxidase method, 2-hour glucose tolerance test, c-peptide fasting, and c-peptide postglucose determinations. In addition, serum levels of cholesterol, triglycerides, high-density lipoprotein, very low-density lipoprotein, low-density lipoprotein, and creatinine were measured. Urinalysis with semiquantitative glucose measurements on both fasting and postglucose load specimens were included. A variety of other metabolic parameters were obtained on a multichannel analyzer utilizing fasting serum.

A data set was created for each patient for each year in the study. Of the total of 122 diabetic patients, 85 had the extensive data set described for the third year. All slit-lamp observations of the cornea were standardized and categorized with coding for localization and grading of changes noted. Fundus photographs were graded for degree of diabetic retinopathy.

In this study keratopathy was defined by the presence of fluorescein staining of the cornea. Epithelial defects ranged from superficial erosions to confluent full-thickness lesions with occasional subepithelial extension. Each cornea was graded as: no stain, minimum staining (several isolated areas showing only punctate erosions), mild, moderate, or severe staining depending upon the progression of punctate epithelial erosions to multiple full-thickness lesions, or to the development of confluent staining patterns. A patient was defined as having keratopathy if either eye showed evidence of mild, moderate, or severe staining. To characterize the patient with keratopathy, each patient was grouped into one of two categories. Those patients who showed evidence of keratopathy any year that they were examined were pooled to create the keratopathy group. Those patients who failed to show keratopathy at any examination were placed into a keratopathy control group. Any eye which had ocular surgery, ie, blepharoplasty, cataract extraction, vitrectomy, retinal detachment surgery, or a filtering procedure, was excluded. Eyes with clinical blepharitis and keratoconjunctivitis were excluded as well as any eye receiving topical medication and showing fluorescein staining. Any eye with a contact lens was also excluded from these groups. All variables relating to the excluded eyes were removed from consideration. All information in a patient's data base was coded in a format that could be analyzed with a Statistical Package for the Social Sciences. Analysis of these data was performed on a Perkin Elmer 3220 computer system through the Biostatistics Department of the Medical College of Wisconsin.

The statistical analysis report includes Student's t-test for difference between two means and Pearson correlation coefficients (r) for degree of association between two variables. Multivariate techniques include analysis of covariance. This method allows statistical adjustment of the dependent variable to eliminate the effects of a confounding variable, such as age. The other multivariate technique used was stepwise multiple regression. In this procedure, the independent variable that explains the greatest amount of variance in the dependent variable is entered on the first step. On subsequent steps, the variable that explains the greatest amount of variance in conjunction with the previously selected variables is entered next. If two independent variables are highly associated with each

other and with the dependent variable, the inclusion of one will probably preclude the inclusion of the other since the unique contribution of the second variable will be small.

RESULTS AND INTERPRETATION

For the overall analysis, all information from the most current year record for each patient was incorported into a separate file. Initially, there were 122 diabetic patients, of which 61 were in the keratopathy group and 51 were in the nonkeratopathy group. Ten patients were excluded because of ocular surgery or contact lens wear. Ten additional patients were excluded, six with clinical blepharitis or keratoconjunctivitis and four patients who were using topical medications and showed fluorescein staining. The final population for consideration thus consisted of the following: 77 adult onset diabetics and 25 juvenile onset diabetics. Forty-four patients (43.1%) with adult onset diabetes had keratopathy and 33 patients in this group (32.4%) did not show keratopathy. When both groups were combined, 51 patients (50%) showed keratopathy and 51 patients (50%) did not. There were 38 males and 64 females in this patient population with an even distribution between the keratopathy and non-keratopathy groups according to sex. Racial distribution revealed 63 white patients and 39 nonwhite patients (Table I).

Table II reveals a significant difference in mean ages of patients with and without keratopathy, but the duration of the disease is not significantly different in these two groups. The presence of distinct corneal epithelial lesions shows clear association with decreased vibration sensation thresholds in both upper and lower extremities; and there is also clear

TABLE I: KERATOPATHY GROUPS BY TYPE OF DIABETES, SEX, AND RACE

	WITH KERATOPATHY (%)	WITHOUT KERATOPATHY (%)	BOTH PATIENT GROUPS COMBINED (%)
Type of diabetes			
AODM*	44 (43.1)	33 (32.4)	77 (75.5)
JODM†	7 (6.9)	18 (17.6)	25 (24.5)
AODM + JODM	51 (50.0)	51 (50.0)	102 (100.0)
Sex			
Male	19 (18.6)	19 (18.6)	38 (37.2)
Female	32 (31.4)	32 (31.4)	64 (62.8)
Race			
White	35 (34.3)	28 (27.5)	63 (61.8)
Nonwhite	16 (15.7)	23 (22.5)	39 (38.2)

*AODM = Adult onset diabetes mellitus.
†JODM = Juvenile onset diabetes mellitus.

association with decreased tear breakup time, Schirmer's II test, and serum triglycerides.

Table II also shows the simple correlations of age and examination parameters. Those variables which correlate with age are vibration sensation thresholds, tear breakup time, Schirmer I and Schirmer II tests, and c-peptide fasting and c-peptide stress measurements. If adjustments for age are made, some of these relationships persist and others do not, eg, c-peptide fasting becomes significant when adjusting for age. Those measurements that lose significance are the Schirmer's II test, vibration perception threshold (finger), tear breakup time, and serum triglyceride levels. Thus, after adjusting for age, we found significant relationships between vibration perception threshold (toes) and keratopathy; and between keratopathy and measurements of c-peptide fasting. A significant relationship was not found between the presence of keratopathy and decreased corneal sensation.

The relationship of vibration perception in the toe and finger and corneal fluorescein staining groups is shown in Figs 4 and 5. The fluorescein staining groups correspond with the degree of keratopathy, ie, group 0 showed no staining, group 1 had minimum staining, group 2 had mild staining, group 3 had moderate staining, and group 4 showed severe staining.

Analysis of covariance was used statistically to adjust the groups for initial differences in age (Table II). After the effect of age had been statistically removed, there remained significant differences between the groups with regard to vibratory perception in the toe ($P < 0.001$) and in the finger ($P < 0.02$). Furthermore, there was a strong linear trend between diminished vibratory perception and degree of keratopathy in both the toe and the finger ($P < 0.01$). In addition, significant differences in mean corneal sensation among the groups were found ($P < 0.04$). The test for linear trend, however, revealed no significant linear component and there were no significant differences among the groups with regard to duration of disease, Schirmer I, Schirmer II, tear breakup time, hemoglobin Alc levels, fasting blood sugar, c-peptide stress, c-peptide fasting, or serum triglyceride levels.

Table III presents the correlation matrix for the following variables: duration of diabetes, corneal sensation, and vibratory perception in the finger and toe. All pairwise correlation coefficients are statistically significant with the exception of the correlation between vibratory perception in the finger and duration of diabetes. The same relationships were significant after adjusting for age. Corneal sensation threshold varies inversely with duration of disease and vibratory perception threshold; ie, dimin-

TABLE II: OCULAR, NEUROLOGIC, AND METABOLIC EXAMINATION DATA BY KERATOPATHY GROUP

	WITH KERATOPATHY MEAN ± SD (*n*)	NO KERATOPATHY MEAN ± SD (*n*)	SIGNIFICANCE OF *t*: *P* <	CORRELATION WITH AGE: *r*	SIGNIFICANCE OF *r*: (AGE) *P* <	SIGNIFICANCE OF *t*: (AGE ADJUSTED) *P* <
Age (yr)	57.47 ± 12.58 (51)	48.43 ± 17.29 (51)	0.003			
Duration (yr)	15.94 ± 9.49 (51)	16.04 ± 10.51 (51)	NS	−0.039	NS	NS
Vibration perception; toe (V)	23.88 ± 15.16 (41)	11.97 ± 10.10 (27)	0.001	0.299	0.007	0.005
Vibration perception; finger (V)	8.85 ± 9.96 (40)	5.02 ± 1.97 (27)	0.021	0.263	0.015	NS
Corneal sensation (mm)	5.63 ± 0.74 (51)	5.71 ± 0.92 (51)	NS	0.003	NS	NS
Schirmer I (mm)	11.23 ± 7.71 (51)	11.37 ± 5.51 (51)	NS	0.347	0.001	NS
Schirmer II (mm)	13.21 ± 7.79 (50)	16.55 ± 7.93 (48)	0.038	0.292	0.002	NS
Tear breakup time (sec)	18.05 ± 10.66 (50)	23.86 ± 12.82 (48)	0.016	0.192	0.029	0.057
Hemoglobin Alc (%)	9.23 ± 2.53 (43)	9.51 ± 2.26 (30)	NS	0.082	NS	NS
Fasting blood sugar (mg/dl)	218.66 ± 89.50 (44)	211.63 ± 76.76 (40)	NS	0.023	NS	NS
C-peptide fasting (ng/ml)	2.98 ± 1.53 (39)	3.36 ± 2.82 (27)	NS	0.407	0.001	0.025
C-peptide stress (ng/ml)	4.41 ± 2.43 (38)	3.81 ± 3.15 (26)	NS	0.501	0.001	NS
Triglycerides (mg/dl)	203.22 ± 95.92 (37)	115.27 ± 83.34 (27)	0.032	0.049	NS	0.057

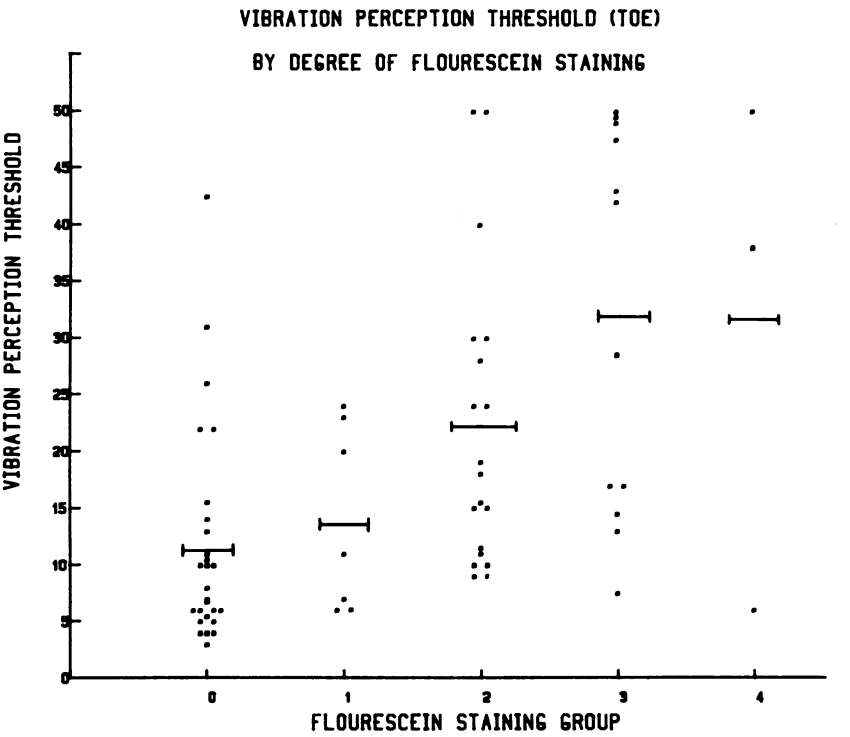

FIGURE 4
Vibration perception of great toe related to degree of corneal staining in diabetic patients.

ished corneal sensation is directly related to diminished vibration perception and a longer duration of disease. Furthermore, duration of disease correlates positively with diminished vibration sensation and decreased vibration perception in the finger varies directly with decreased vibration perception in the toe.

Table IV summarizes the stepwise regression analysis performed on the two dependent variables: the keratopathy group and corneal fluorescein staining group. Potentially independent variables included age, type of diabetes (adult onset or juvenile onset), duration of disease, vibration perception (finger and toe), corneal sensation, Schirmer II test, tear breakup time, c-peptide fasting, and serum triglyceride levels. These variables were selected into the regression analysis so long as their unique contribution added significantly to the prediction of the dependent variable under consideration. R^2 is the amount of variation in the dependent variable that is due to the independent variables in each step.

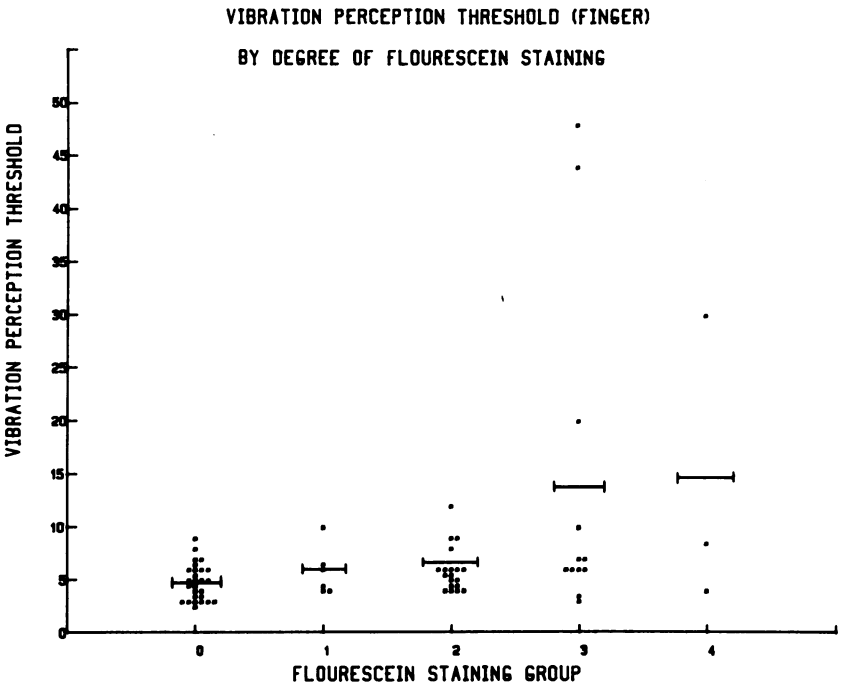

FIGURE 5
Vibration perception of index finger related to degree of corneal staining in diabetic patients.

The strongest predictor of both keratopathy and corneal fluorescein staining was vibration perception threshold in the toe ($P < 0.01$). The only other variable which contributed significantly to the prediction of corneal fluorescein staining was tear breakup time ($P < 0.03$). All other variables had no significant individual contribution to the regression.

In addition to vibration perception in the toes, other predictors of keratopathy were type of diabetes ($P < 0.01$) and c-peptide fasting ($P < 0.01$). No significant relationships were found between the presence of keratopathy and tear glucose levels, endothelial cell densities, corneal thickness measurements, and the presence of *Staphylococcus epidermidis* on either the lid margins or the conjunctiva.

Table V shows that a high percentage of all eyes in this study demonstrated the presence of *S epidermidis* from conjunctival cultures. It should be emphasized, however, that 86% of patients in the keratopathy group were asymptomatic with respect to the type of complaints typically

TABLE III: CORRELATION MATRIX OF DURATION OF DIABETES, CORNEAL SENSATION, AND VIBRATORY PERCEPTION IN FINGER AND TOE

	DURATION OF DIABETES	VIBRATORY PERCEPTION; TOE	VIBRATORY PERCEPTION; FINGER
Corneal sensation			
r	−0.255	−0.401	−0.224
(*n*)	(102)	(68)	(67)
P <	0.005	0.001	0.034
Duration of diabetes			
r		0.236	−0.045
(*n*)		(68)	(67)
P <		0.03	0.486
Vibratory perception (toe)			
r			0.508
(*n*)			(67)
P <			0.001

associated with staphylococcal keratoconjunctivitis. Furthermore, analysis of these data show that 58 of 167 eyes (34.7%) in the keratopathy group showed positive conjunctival cultures and 55 of 159 eyes (34.6%) in the group without keratopathy also showed *S epidermidis* on culture. This was true in both the adult onset diabetes mellitus and the juvenile onset diabetes mellitus groups of patients. With respect to cultures of the lid margin (Table VI), *S epidermidis* was present in almost equal percentages (98.2% vs 98.1%) in both the keratopathy and nonkeratopathy groups. The isolation of other organisms and culture techniques using other media will be presented in a separate publication.

DISCUSSION

Corneal epithelial lesions can be found in approximately one-half to two-thirds of all patients with diabetes mellitus. These lesions vary in depth, extension, and distribution. They are transient and clinically resemble the keratopathy seen in chronic staphylococcal keratoconjunctivitis. Eighty-six percent of patients in this study, however, did not have symptoms characteristic for staphylococcal keratitis and, indeed, these microorganisms could be isolated in equal percentages from diabetic patients without keratopathy. It is reasonable to conclude that diabetic keratopathy is a separate and distinct entity and its presence appears clearly related to peripheral neuropathy. Furthermore, our data show that the severity of keratopathy is directly related to the degree of diminution of peripheral sensation occurring in diabetes. Diabetic keratopathy, therefore, probably represents a form of corneal neuropathy.

TABLE IV: MULTIPLE REGRESSION ANALYSIS SUMMARY OF KERATOPATHY GROUP AND CORNEAL FLUORESCEIN STAINING GROUP

DEPENDENT VARIABLE	INDEPENDENT VARIABLE	PEARSON CORRELATION COEFFICIENT (r)	R^2	F VALUE*	DEGREES OF FREEDOM
Corneal fluorescein staining group	Vibratory perception (toe)	0.502	0.252	20.54	1,61
	Tear breakup time	−0.248	0.308	13.32	2,60
Keratopathy group	Vibratory perception (toe)	0.403	0.162	11.82	1,60
	Types of diabetes	0.351	0.252	10.12	2,60
	C-peptide fasting	0.095	0.335	9.91	3,59

*$P < 0.01$.

TABLE V: BACTERIAL CULTURE RESULTS* (POOLED FOR YEAR 1 AND YEAR 2)—IN DIABETIC PATIENTS WITH AND WITHOUT KERATOPATHY

ORGANISM (CONJUNCTIVA)	KERATOPATHY		NO KERATOPATHY	
	NO EYES	(%)	NO EYES	(%)
Staphylococcus epidermidis	58/167	(34.7)	55/159	(34.6)
Corynebacterium sp	22/167	(13.2)	26/159	(16.4)
Other	8/167	(4.8)	7/159	(4.4)
No growth	94/167	(56.3)	90/159	(56.6)

*The following were excluded: Eyes with clinical blepharitis, keratoconjunctivitis, previous surgery, and contact lens wear.

Factors such as age, decreased tear breakup time, reduced tear production, and perhaps the degree of metabolic control are related to the predictability of keratopathy, but their effects are interrelated and none of these factors alone can be isolated as the sole predictor of corneal epithelial lesions seen in diabetic patients. Significant relationship was not found between the presence of keratopathy and reduced corneal sensation. Perhaps this is due to the relative insensitivity of methods available to measure corneal sensation. Diminished corneal sensation is directly related, however, to diminished vibration perception and to duration of disease. This relationship exists only in those patients with keratopathy.

The presence of diabetic keratopathy is not associated with tear glucose levels, reduced endothelial cell densities, increased corneal thickness measurements, or with the duration of diabetes; although the duration of disease may have an influence on the presence of associated factors such as peripheral neuropathy and tear breakup time. Similarly, the level of metabolic control in diabetes seems related to the predictability of keratopathy and this may reflect a relationship between metabolic control and the development of both peripheral neuropathy and reduced corneal sensation. Recently, the role of metabolic control in influencing corneal

TABLE VI: BACTERIAL CULTURE RESULTS* (POOLED FOR YEAR 1 AND YEAR 2)—IN DIABETIC PATIENTS WITH AND WITHOUT KERATOPATHY

ORGANISM (LID MARGINS)	KERATOPATHY		NO KERATOPATHY	
	NO EYES	(%)	NO EYES	(%)
Staphylococcus epidermidis	165/168	(98.2)	156/159	(98.1)
Corynebacterium sp	19/168	(11.3)	26/159	(16.3)
Staphylococcus aureus	12/168	(7.1)	15/159	(9.4)
Other	26/168	(15.5)	24/159	(15.1)
No growth	3/168	(1.8)	3/159	(1.9)

*The following were excluded: Eyes with clinical blepharitis, keratoconjunctivitis, previous surgery, and contact lens wear.

sensation has been experimentally demonstrated in diabetic dogs.[11] Clinically, this concept is an important one and also relates to the recent work by the Steno Study Group[12] which suggests that long-term control of diabetes, achieving near-normal blood glucose levels, may arrest or even reverse some of the features associated with diabetic microangiopathy.

It is interesting to note that no cases of recurrent epithelial erosion were noted in this group of 122 patients during the entire study period of 3 years, and the characterization of diabetic keratopathy offered by this study does not explain the recurrent erosion syndromes which have been reported following surgical trauma to the corneal epithelium of diabetic patients.[13] It is possible that partial corneal denervation plays a role in fragility and delayed adherence of corneal epithelium following trauma; however, several laboratory studies suggest that other mechanisms are probably involved. For example, electron microscopic studies show that damage to the corneal epithelium produced by freezing removes the basement membrane as well as epithelium in alloxan-induced diabetic rabbits but not in nondiabetic controls.[14] An abnormal or damaged basement membrane following trauma would obviously affect both regeneration of epithelium and the adherence of regenerated epithelium.

SUMMARY

Corneal epithelial lesions can be found in approximately one-half of asymptomatic patients with diabetes mellitus. These lesions are transient and clinically resemble the keratopathy seen in staphylococcal keratoconjunctivitis. Staphylococcal organisms, however, can be isolated in equal percentages from diabetic patients without keratopathy. Diabetic peripheral neuropathy was found to be related to the presence of diabetic keratopathy after adjusting for age with analysis of covariance. The strongest predictor of both keratopathy and corneal fluorescein staining was vibration perception threshold in the toes ($P < 0.01$); and the severity of keratopathy was directly related to the degree of diminution of peripheral sensation. Other predictors of keratopathy were: reduced tear breakup time ($P < 0.03$), type of diabetes ($P < 0.01$), and metabolic status as indicated by c-peptide fasting ($P < 0.01$). No significant relationships were found between the presence of keratopathy and tear glucose levels, endothelial cell densities, corneal thickness measurements, the presence of *S epidermidis*, or with duration of disease. It is our conclusion that asymptomatic epithelial lesions in the nontraumatized diabetic cornea can occur as a manifestation of generalized polyneuropathy and probably represent a specific form of corneal neuropathy.

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DISCUSSION

DR PETER R. LAIBSON. Doctor Schultz and co-workers continue to study diabetic corneal neuropathy which they reported on at the American Ophthalmological Society Meeting 2 years ago. They studied 120 patients for 1 year and concluded that diabetic corneal changes are present in 47% to 64% of patients at any given time. Corneal sensation was reduced in 18% of the patients with 47% having decreased tear production and 94% showing *Staphylococcal epidermidis* on the lid margin.

This study further extends their work to 3 years in these patients. Eighty-five of the 120 patients initially examined returned for third-year examinations. This is an excellent follow-up on this group of diabetic patients. Eyes with clinical blepharitis, keratoconjunctivitis, or those receiving topical medication with fluorescein staining as well as patients using contact lenses were excluded from the evaluation of corneal staining in diabetics. Their final population consisted of 77 adult onset diabetics and 25 juvenile diabetics after several more patients were added to the study groups. Forty-three percent of adult onset diabetics had keratopathy and after adjusting for age they found significant relationship be-

tween vibration perception, threshold, and keratopathy as well as between keratopathy and measurements of fasting c-peptide levels. It was interesting that significant relationship was not found between the presence of keratopathy and decreased corneal sensation.

There continued to be a very high percentage of patients who demonstrated the presence of *S epidermidis* on lid margins and in conjunctival culture, although 86% of the patients in the keratopathy group were asymptomatic with regard to complaints associated with staphylococcal blepharo-keratoconjunctivitis. *S epidermidis* was present in almost equal percentages in both the keratopathy and nonkeratopathy groups.

The authors concluded that it was reasonable to state that diabetic keratopathy is a separate and distinct entity and at present appeared clearly related to peripheral neuropathy. Also the severity of the keratopathy was directly related to the degree of diminution of peripheral sensation occurring in their diabetic patients. They could not explain the fact that reduced corneal sensation did not correlate with the presence of keratopathy and they stated that the relative insensitivity of the methods available to measure sensation might have been the reason for this. It was also extremely interesting to note that there were no cases of recurrent epithelial erosion in their study group during the entire 3-year period of observation. Therefore they felt their results did not explain the recurrent erosion syndromes reported following surgical and nonsurgical trauma to the cornea in diabetic patients.

In another study from the same center, MacCrae and associates studied experimentally produced diabetic dogs and normal dogs. They found that poorly controlled diabetes in the canine of long-standing duration caused a significant reduction in corneal sensitivity which might make these corneas more susceptible to damage from ocular surgery or contact lens use. They only measured corneal sensitivity with the anesthesiometer described by Cochet and Bonnet, the same instrument used by Doctor Schultz and associates. They were unable to detect a significant decrease in sensitivity in poorly controlled diabetic dogs which seemed to improve as the diabetes was better controlled. It would have been interesting for them also to check the slit-lamp appearance of the cornea for diabetic keratopathy which the present authors found so common in their diabetic patients. (*Cornea* 1982; 1:223-226.)

Ishida and associates recently studied corneal innervation in diabetic rats. They too pointed out that a decreased corneal sensitivity has been observed in diabetics and postulated that alterations of innervation might be responsible for it. They experimentally induced diabetes in rats by injecting streptozotocin (65 mg/kg) which caused diabetes. Animals were sacrificed at 1 week, 4 weeks, 16 weeks, and 36 weeks and the results reported at the Association for Research in Vision and Ophthalmology Meeting in Sarasota, Florida, on Friday, May 6, 1983. They found some changes at 16 weeks in the nerve beading with increased irregularity. It increased at 36 weeks. At 16 weeks there was beginning of Schwann cell disease and at 36 weeks more severe changes of Schwann cell disease with irregularity in

the thickness of the basement membrane of the Schwann cell noted. There was also axonal degeneration in the Schwann cell. This study correlated with the work of MacCrae and associates to show that there is definite nerve damage in the peripheral cornea after experimentally induced diabetes.

The continued work of Doctor Schultz and co-authors on diabetic corneal neuropathy has alerted us to this entity in diabetic patients. The clinical impression is that the diabetic neuropathy may be secondary to decreased corneal sensation in the human. The experimental work in diabetic animals definitely has shown nerve damage in these corneas. It would be worthwhile to examine autopsy specimens of humans who die with severe diabetes to look at the peripheral corneal nerves to determine the status of these nerves in the human as well. Another way to correlate these two findings would be to try to examine diabetic animals and rodents that are experimentally made diabetic to see if their corneas also might show a diabetic type of corneal neuropathy compared to the normal. The authors are to be encouraged to continue this work.

Dr Walter Stark. Let me congratulate the authors on their fine presentation and the tremendous amount of very good work. I would like to share with you some work that is being done at the Wilmer Institute and at the National Eye Institute by one of our fellows, Doctor Datiles, who is doing a combined fellowship with us and at the NIH with Doctors Kupfer and Kinoshita. Doctor Kinoshita, of course, is one of the world's experts on aldose reductase inhibitors and their application in diabetics. We are familiar with the hexokinase shunt which produces the glucose-6-phosphate from glucose in normal pathways, but in the diabetic there is often an overloading of this system with productions of polyols, and, in particular sorbitol alcohol which has been incriminated as a cause of cataract formation in certain diabetic animals and probably in human diabetics. There is a considerable amount of research work now going on with the use of aldose reductase inhibitors, and in particular, sorbinil, which blocks the shunt leading to excess sorbitol formation. This has been shown in the diabetic animals to prevent or delay cataract formation and in the human situations clinical trials are currently underway to see if this reduces the formation of cataracts in the diabetic. The beneficial effects of aldose reductase inhibitors have also been shown in the treatment of diabetic peripheral neuropathy. Doctors Datiles and Kinoshita have looked at the corneal epithelium in the diabetic animals and with special stain have shown the presence of this enzyme, aldose reductase, in the basal corneal epithelial cells. The application of this finding was carried out by Doctors Kinoshita, Kupfer, and Datiles in diabetic animals where they cause corneal epithelial erosion and show that there was a delay in healing as compared with the normal control. However, if they abraded the corneal epithelium of the same diabetic animal and treated that eye with topical aldose reductase inhibitors, the corneal epithelium healed exactly the same as in the nondiabetic control. Using this information to develop studies for the use of aldose reductase inhibitors, Doctor Datiles has recently reviewed our contact lens patients and found that the patients with diabetes had a

much greater rate of problems with extended-wear aphakic contact lenses than age-matched control patients. Fifty-eight percent of the patients with diabetes had problems of the epithelium, whereas in the nondiabetic patients only 38% had problems. Therefore, this appears to be an important area of work and it is possible that the aldose reductase inhibitors could be used in clinical trials to study cornea as well as the peripheral neuropathy as has been nicely demonstrated by Doctor Schultz in this paper.

DR ALBERT RUEDEMANN. I would like to add one point. When the contact lens wearer is a diabetic, I think we should remember that their hand coordination for the contact lens may be reduced and these people are liable to create a problem just by manipulating the lens on their eye.

DR RICHARD O. SCHULTZ. Thank you, Doctor Laibson, Doctor Stark, and Doctor Ruedemann for your comments. In response to Doctor Laibson: The presence of keratopathy did not correlate statistically with reduced corneal sensation in this study, but I think this is a reflection of the relative insensitivity of the methods available to measure corneal sensation. There is no question that we have excellent correlation between diminished vibration perception in the extremities and the presence of keratopathy; and the techniques that are used to measure vibration perception are extremely sensitive.

Doctor Stark mentioned the possible use of topical aldose reductase inhibitors in diabetic keratopathy. I think there is increasing evidence to indicate that accumulation of sorbitol in the peripheral nerves may account for diabetic peripheral neuropathy and aldose reductase inhibitors may have a place in treating that part of the diabetic problem. If the corneal changes described in this paper are the result of peripheral neuropathy, this might offer a method of treatment. I think Doctor Stark is referring, however, to the beneficial effects of aldose reductase inhibitors on epithelial regeneration in the diabetic cornea; and this effect is based on the presence of sorbitol in the epithelium of diabetic animals. In this regard we have looked for the presence of sorbitol in the human diabetic corneal epithelium and initially thought we could isolate this substance along with other high molecular weight sugars. However, with more refined methods of testing we did not find sorbitol even in pooled specimens of corneal epithelium obtained during surgery.