Polymorphic stromal dystrophy

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Strachan (1968) described a bilateral corneal dystrophy in a 62-year-old man, characterized by punctate, irregular opacities located mainly in the deepest layers of the cornea.

The middle and superficial layers were involved to a lesser extent. The size and density of the lesions were sufficient to produce a distorted view of the fundus and to break up the red reflex. Some of the larger opacities produced stromal protuberances which made the posterior surface of the cornea irregular. The corrected visual acuity was 6/12 part in each eye. Strachan regarded the disorder as a form of pre-Descemet's dystrophy. An apparently related disorder was described by Pillat (1939) in a girl whose corneae showed deep, punctate stromal opacities of varying size, blue-grey in appearance on focal illumination, and more or less transparent on retroillumination. A sister showed an additional change in

the form of numerous glass-like lines arranged radially in the anterior layers of the peripheral corneal stroma. Visual acuity was slightly decreased and corneal sensation normal and there was no inflammatory background. Pillat regarded the disorder to be an inherited dystrophy.

Between September, 1971, and May, 1973, we have observed nine patients whose corneae have shown to a greater or lesser degree changes similar to those described by these authors.

Methods of study

Each patient was examined on a number of occasions, when a detailed history was taken and the ocular findings documented. Corneal changes were recorded with drawings and by slit-lamp (Zeiss) and macro-photography (Brown, 1970). Corneal thickness was measured with a Goldmann pachymeter. Measurements of the size of lesions were made from selected macrophotographs and are detailed in Table I.

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Table I *Dimensions of corneal features in polymorphic stromal dystrophy*

<i>Feature</i>	<i>Measurement</i>	<i>Patient</i>	<i>No. of eyes</i>	<i>Dimension</i>
Polymorphic flakes	Horizontal diameter	Case 3	1	30μ (12-102) n = 62
		Case 5	1	43μ (14-106) n = 23
		Case 3	1	46μ n = 62
	Density of flakes per mm ²	Case 5	1	17 n = 23
		Case 6	1	29 n = 180
		Case 6	1	194 n = 2
Endothelial depressions	Vertical diameter	Case 6	1	128μ n = 2
		Case 7	1	159μ n = 2
Filamentous opacities	Diameter of: 1° branch 2° branch 3° branch			40μ (2/2)†
				24μ (5/3)†
				15μ (2/2)†

* n = number of features counted.

† Figures in parentheses: Numerator = number of zones selected.

Denominator = number of patients in whom readings were made.

FIG. 1 *Distribution and levels of stromal opacities in polymorphic stromal dystrophy*

Clinical findings

The characteristic features of the cornea observed were punctate and filamentous stromal opacities occupying a discoid axial zone (Fig. 1). In the least developed cases there were fine opacities lying in the most posterior stroma without the presence of filaments (1a). In others a few filaments were present in addition (1b). In one case the posterior spots and some filaments were arranged in the form of a ring (1c) and in another case only the anterior stroma was affected in an annular zone (1d). In two patients the full thickness of the stroma was involved by punctate opacities, and in one, filaments were also present (1e).

The biomicroscopical features of individual opacities, punctate or linear, were the same in the different patients observed. The punctate opacities were polymorphic, grey-white, and slightly refractile in focal illumination; they were relatively transparent in retroillumination and showed reversed transillumination features (Brown, 1971) (Figs 2 and 3). They varied in form from fleck-like lesions to stellate, linear, and irregular configurations reminiscent of snowflakes. Most lesions were discrete but confluent lesions were also present. In diameter, the lesions varied from $12\ \mu$ in the smallest lesions to $106\ \mu$ in the larger lesions (Table I). Posteriorly, in the region of Descemet's membrane, the flecks consistently appeared to push back the endothelium to produce a depression convex towards the anterior chamber (Fig. 4). The flecks were here separated from the endothelium by a clear zone. On low-power bio-

FIG. 2 *Polymorphic stromal opacities viewed against the red reflex*

microscopical examination in the zone of specular reflection, these dimples strongly resembled cornea guttata but were of greater size. On examination of the endothelial mosaic under high magnification ($\times 40$ Zeiss), the endothelium both within and outside the depressions was normal for age in appearance. In general the punctate opacities were largest posteriorly and axially and finest peripherally and in the more anterior stroma.

The filamentous opacities were also faintly grey in focal illumination and refractile in retroillumination. The filaments showed irregular beading or longitudinal striations. Occasional dichotomous branching at their central ends gave rise to secondary and tertiary branches (Fig. 5). The diameters of filaments are given in Table I. Filaments varied from 15 to 40 μ in diameter.

FIG. 3 Individual fleck-like stromal lesions. Retroillumination against the iris

In the majority of patients, the stroma intervening between each type of opacity was entirely normal, corneal thickness was normal, corneal reflexes were normal, the epithelium was intact, and there was no fluorescein staining. Where significant reduction of vision was present factors other than the corneal dystrophy appeared to be responsible. This applies in Case 2 (corneal scarring), Cases 1, 2, 3, 4, and 6 (cataracts), and Cases 5 and 7 (squint amblyopia). In Case 7 the left non-amblyopic eye had a corrected

visual acuity of 6/9 despite involvement of the whole stromal thickness in the dystrophic process. In Case 6, in which the full thickness of stroma was also involved, the visual acuity was 6/12. In the last case, it is felt that both the corneal disorder and early lens opacities contributed to the modest visual disturbance.

FIG. 4 Indentations of endothelium produced by posterior stromal lesions. Note normal hexagonal endothelial mosaic

In general it may be said that, where the dystrophy involves the visual axis, the visual acuity is not reduced by more than one line.

Case reports

Case 1, an 84-year-old Caucasian male, came to Moorfields Eye hospital in September, 1972, with an attack of angle-closure glaucoma precipitated by an

FIG. 5 *Beaded and branched filamentous opacities and fleck-like lesions seen by retroillumination*

intumescent cataract. A preoperative examination revealed, in addition, bilateral flake-like stromal opacities of the type described above. These occupied predominantly the posterior third of a discoid zone of the stroma 5.5 mm in diameter in the right eye and 4.5 mm in the left. A few similar opacities were present at the level of Bowman's membrane. No filaments were visible. Visual acuity was 6/18 in the right eye with -0.5 D sph. and perception of light in the left eye. The reduction of vision was attributed to cataracts in each eye. Corneal thickness was 0.55 mm in each eye. The anterior corneal surface was smooth, and there was no corneal stain. Ocular pressure was controlled medically, and uneventful cataract surgery at a later date did not alter the appearance of the corneal lesions.

Case 2, a 76-year-old Caucasian female, was referred because of a 3-months history of left epiphora and of a foreign body sensation in the left eye. A left corneal ulcer had been treated in 1940.

Examination

In November, 1971, there was vascularization of the upper left corneal scar with some staining at the surface and a nodular superficial opacity in the 10 o'clock meridian.

Visual acuity was 6/12 in the right, with $+1$ D sph., $+0.75$ D cyl., axis 150° , and 6/60 in the left, with $+0.5$ D sph., $+0.75$ D cyl., axis 25° . The right cornea was entirely normal apart from the presence of numerous fine stellate opacities occupying an axial discoid zone of the posterior third of the stroma. The most posterior opacities indented the endothelium. The left cornea, apart from the scarring already noted, showed a solitary pre-Descemet's punctate opacity. The right corneal reflex was normal and the left reduced over the scar. Axial corneal thickness was 0.52 mm right and 0.54 mm left.

Case 3, a 51-year-old Ugandan Asian female, presented in January, 1973, complaining of deterioration of vision in both eyes for the previous 6 months. She had been diabetic for 13 years and treated with Tolbutamide until her arrival in the United Kingdom 4 months previously. Her treatment was then changed to insulin.

Examination

The corrected visual acuity was 6/18 in each eye (with right -3 D sph. and left -2.5 D sph.). Stromal changes were readily identifiable. The opacities were concentrated in a ring-like distribution leaving the central zone of the

cornea relatively clear. The density of the opacities decreased peripherally and anteriorly. The opacities were predominantly punctate with very few of the linear variety, the most posterior opacities indenting the corneal endothelium in the characteristic manner. Corneal sensation and tear film were normal as were the epithelial and endothelial layers. Central corneal thickness was 0.50 mm on the right and 0.45 mm on the left. The patient had a moderate and symmetrical degree of nuclear sclerosis sufficient to account for the degree of visual loss. The retinae showed dilated and rather tortuous veins with arterio-venous nipping but, apart from this, no overt signs of diabetic retinopathy. The maculae appeared normal. The only other findings were signs of mild Stage IV trachoma in each eye.

Case 4, a 70-year-old Caucasian male, presented in May, 1966, complaining of a blur before the right eye. The visual acuity was 6/12 in each eye, with +4.5 D sph., +0.75 D cyl., axis 120° in the right, and +4.5 D sph., +0.75 D cyl., axis 75° in the left. The visual disturbance was attributed to cortical cataracts. It was noted that each cornea showed a bilateral disturbance of the posterior stroma occupying a central discoid zone together with changes annotated as cornea guttata. When he was first seen by the authors in September, 1971, the visual acuity was unchanged and the following corneal signs were noted. The discoid zone in the posterior one third of the stroma was occupied by punctate polymorphic opacities. The lesions previously referred to as cornea guttata were seen to be indentations of Descemet's membrane by the deepest stromal opacities, with normal overlying endothelium. The zone of involvement measured 6.3 mm horizontally by 5.3 to 5.5 mm vertically. A lesser number of scattered filamentous opacities were also present, some branched, and all reminiscent of the filamentous opacities of lattice dystrophy. The filaments were more anteriorly and peripherally placed than the majority of the polymorphic flecks. In addition to these features, Bowman's membrane exhibited a swirled translucent appearance and also in each cornea there was a small number of round defects at the level of Bowman's layer with well-defined edges filled by epithelial facets. There were eleven such "Swiss cheese" defects in the right cornea and six in the left cornea (Fig. 5); they were in the region of 0.4 mm across. An ill-defined change was also seen in the peripheral cornea in each eye in the region of Descemet's membrane and consisting of fine parallel striae running in radially from the region of the limbus for a few millimetres. Each cornea showed a moderate arcus senilis and Vogt's limbus girdle change. The corneal surface appeared smooth and the corneal reflexes were normal in each eye. Axial corneal thickness was 0.50 mm right and 0.49 mm left. Ocular pressures were 18 mm.Hg in each eye by applanation. Gonioscopy was normal and the fundi were normal. A study of the notes suggested that no definite change in the corneal appearances had occurred in the period from 1966 to September, 1971. The blood picture and serum cholesterol were normal and the Wasserman reaction was negative.

Case 5, a 65-year-old Caucasian female, complained of a deterioration of vision since the summer of 1971 and of some soreness in the right eye. She had been treated with

gold and cortisone therapy for one year for severe rheumatoid arthritis, which had developed in 1970 after infection with rubella. The patient suffered a Bell's palsy in 1968 and in childhood had tuberculosis and anaemia. Her mother was blind as a result of cataract and detached retina, and her sister was short-sighted.

Examination

The visual acuity was 6/60, with -8.0 D sph. right, and 6/12 with -3 D sph. left. That in the right eye had been poor since childhood presumably because of anisometropic amblyopia. She had a 15° right divergent squint. Each cornea exhibited an axially situated discoid zone of polymorphic flecks in the posterior third of the stroma. The paracentral portion of this zone was relatively free of lesions on each side. On each side the posterior opacities produced backward indentations in the endothelium. The right cornea showed some fine beaded nerve-like branching filaments. These were absent from the left cornea. Apart from a mild peripheral beaten appearance, the endothelium was normal. The epithelium and remaining stroma and Bowman's zone were normal apart from the presence of Vogt's limbus girdle changes. The corneal reflexes were normal. Axial corneal thickness was 0.54 mm right and 0.52 mm left. The anterior chamber, angles, lens, vitreous, and fundi were entirely normal. The intraocular pressure was 22 mm.Hg right, and 21 mm.Hg left, by applanation.

Case 6, a 70-year-old-Caucasian male, had no specific complaints other than a deterioration in near vision which became manifest in 1960 and had been alleviated by appropriate changes in his spectacles. There was no relevant past ocular history. The patient suffered from bronchitis and there had been recent weight loss and some unsteadiness in gait. There were no recorded visual problems in the family history but the patient's father had died of tuberculosis and his daughter suffered pulmonary tuberculosis, whilst her son had suffered from tuberculous meningitis.

Examination

In February, 1972, the corrected visual acuity was 6/12, with +3 D sph. in the right eye, and 6/12, with +2.25 D sph. in the left. The corneal appearances were roughly symmetrical. The corneae showed a discoid zone in the stroma, about 6 mm in diameter, containing multiple polymorphic grey-white snowflake opacities, greatest in density behind but also involving the anterior stroma. A few were crystal-like. In addition, there were multiple linear, nodular, branching striae at all levels in the stroma. The finest were found centrally and they were most marked at the periphery of the discoid zone. The discoid zone showed a mild stromal haze and there were some hazy opacities about the nerve-like filaments. Apart from a small scar, Bowman's zone was free from opacity.

Case 7, a 69-year-old Caucasian male, first attended in July, 1970, with marginal corneal ulceration in the right eye. He also showed several superficial corneal nodules, more numerous on the right than the left, consistent with a diagnosis of Salzmann's degeneration. There was also extensive superficial scarring extending into the anterior stroma of both eyes and associated with Bietti's "lacunar" change in Bowman's membrane (Bietti, 1965). In the full

stromal thickness of both eyes there were numerous polymorphic flecks, some linear, some stellate, and others rather crystalline and suggestive of snowflakes. Many of the flecks appeared agglomerated and confluent in the region of Bowman's membrane. The deepest lesions indented Descemet's membrane. The endothelium was normal in each eye. Corneal sensation did not appear reduced. The corneal thickness was 0.56 mm in each eye, and the tear film was also normal. The ocular media were clear and the fundi normal. The intraocular pressure was normal.

The visual acuity was 6/60 right, with +4 D sph., +2.75 D cyl., axis 80°, and 6/9 left, with +5 D sph., +2 D cyl., axis 135°.

The right eye was apparently amblyopic and this was associated with a squint in infancy.

Both parents had died from tuberculosis whilst the patient was still an infant; the remainder of the family history is unknown.

Case 8, a 50-year-old Caucasian female, known to be suffering from myelomatosis, had been symptom free for a year after a course of radiotherapy when she developed pain and loss of vision in the left eye. Investigation revealed a soft tissue mass in the midline expanding the pituitary fossa, extending anteriorly to the optic canals and down to the paranasal sinuses. Craniotomy and subsequent exenteration of most of the tumour mass (carried out at the National Hospital for Nervous Diseases, Queen Square), relieved the pressure on the left optic nerve and the visual acuity ultimately returned to 6/9 corrected, though with a left temporal hemianopia. The right visual acuity was 6/6 corrected with a full field. The histology of the tumour was that of a plasma cell myeloma.

As a coincidental finding we noted that each cornea contained numerous punctate polymorphic opacities occupying an anterior stromal annular zone, and largely avoiding the visual axis and posterior stroma (Fig. 1*d*). A few branching filaments were also present, mainly anterior to the punctate lesions, with a tendency to radial direction. The degree of involvement was similar in both eyes and the morphology of the lesions apparently identical to those of the other cases described, though the anterior distribution differed from the rest.

Case 9, a Caucasian male in the eighth decade, showed punctate opacities in a tiny zone about 1 mm in diameter in the axial part of the most posterior stroma. Despite the small number of stromal spots present, distinct and typical indentation of the endothelium occurred. No other significant corneal disease was present.

In view of the disordered serum proteins in Case 8 and the known association between dysproteinemia and corneal deposits (Hobbs, 1962), protein analyses were carried out in the first seven cases (see Table III, p. 131).

Two grandchildren, aged 22 and 21 years of the family of Case 6, were examined and found to have normal corneae. The 60-year-old brother of Case 3 had normal corneae. Attempts to locate other family members were unsuccessful.

Discussion

Nine patients, five male and four female, aged 51 to

84 years, are described. The corneal disorder in each case is bilateral, avascular, and (apart from two patients showing other corneal disease) symmetrical and free from inflammatory episodes. For this reason, and despite the lack of information about other family members, it is reasonable to regard the condition as a corneal dystrophy. The apparent late onset of the disorder makes differentiation from a degenerative disorder more difficult and such a possibility must still be entertained.

In the majority of cases described, the corneal dystrophy was a coincidental finding to the presenting ocular or systemic disorder. Though the association between the corneal disorder and other ocular disease might suggest a degenerative aetiology, it is felt that the association was spurious and served to bring to light an otherwise asymptomatic disorder.

It appears that Cases 1, 2, 4, and 9 are identical to the one described by Strachan (1968) and possibly similar to the condition described by Pillat (1939).

Strachan (1968) classified the condition which he described as a pre-Descemet's dystrophy. This would place it in the same category as cornea farinata (Vogt, 1930), deep filiform dystrophy (Maeder and Danis, 1947), deep punctiform dystrophy (Franceschetti and Maeder, 1954), and the group of pre-Descemet's changes described by Grayson and Wilbrandt (1967). The opacities in cornea farinata are dust-like and can be observed biomicroscopically only by retroillumination. In deep filiform dystrophy, larger, corkscrew-like opacities have been observed, sometimes with punctate opacities. Vogt's original patient also had keratoconus, but subsequent patients have been described without keratoconus (Franceschetti, Chodoss, Dieterle, and Forni, 1957). Inheritance is uncertain in these disorders. Deep punctiform dystrophy was described in a case of ichthyosis, and punctate pre-Descemet's changes have been observed in affected members and carriers of X-linked ichthyosis (Sever, Frost, and Weinstein, 1968).

Grayson and Wilbrandt (1966) described a number of patients showing a variety of pre-Descemet's opacities, which they classified as dendritic, boomerang, circular, comma, linear, and filiform types. The opacities were grouped in axial, annular, and diffuse arrangements. The axial and annular arrangements are reminiscent of those observed in our cases. Grayson and Wilbrandt noted the occurrence of their pre-Descemet's disorder in association with corneal disorders such as anterior membrane disease and keratoconus. Dominant transmission of the disorder was observed. In none of their cases was indentation of the endothelium by the opacities noted, and the anterior stroma was not affected. Branching filaments were not described. On these grounds it seems reasonable to regard the disorder described here as a separate condition.

The branching linear opacities are biomicroscopically identical to those which may be seen in lattice dystrophy (Bron and Tripathi, 1974). The punctate stromal opacities are also similar to opacities described in certain families with lattice dystrophy (Dark and Thomson, 1960). The condition which we describe differs from lattice dystrophy in a number of significant features, including late onset, freedom from symptoms, and the presence of normal corneal sensation (Table II).

Table II Differentiation of polymorphic stromal dystrophy from lattice dystrophy

Dystrophy	Polymorphic stromal	Lattice
Age at presentation	Sixth decade	First decade (some later)
Symptoms	Incidental	Pain and visual loss
Lesions at onset	Posterior stroma (some anterior)	Posterior stroma (some mid-)
Corneal reflex	Normal	Diminished
Progression	Slow or none	Marked
Inheritance	Not established	Dominant

It may be noted that, in family 'L' of Dark and Thomson, the lattice dystrophy was of late onset and caused less visual upset, discomfort, and reduction in corneal sensation than the classical variety. In a member of that family observed by one of us (A.J.B.) the lesions did not affect Bowman's membrane, so that the corneal surface was smooth. However, even the deepest lesions did not produce the deep indentations into the endothelium characteristic of our cases. Progression has not been observed in the cases described here even in the patient with the maximum follow-up period of 6 years (Case 4). It is probable that the condition starts in later life and advances

slowly. It has not been described in youth, and in the cases described a variable amount of stroma has been affected. This may reflect the stage of progression reached. The condition described appears to differ from the progressive corneal dystrophy of Waardenburg and Jonkers (1961) by its late onset without clear evidence of progression, absence of painful episodes, and failure to affect the corneal epithelium. It must also be distinguished from the *dystrophie mouchetée* of François and Neetens (1957), in which the stroma exhibits small fleck-like opacities, often oval, round, or ring-shaped, but also more irregular in shape. This latter condition differs from polymorphic stromal dystrophy in that the whole extent of the stroma is involved both laterally and in depth, without preference for the central stroma, and the density of the lesions is much sparser. Also, *dystrophie mouchetée* has been observed in the early years of life. The occurrence of myelomatosis in Case 8, with grossly disturbed immunoglobulins, raises the question whether the corneal changes observed in this condition are simply a manifestation of a dysprotein-aemia. An association between abnormal plasma and urinary proteins on the one hand, and deposits in the corneal stroma on the other was reported by Meesman (1934) and by Blobner (1938). Changes have been found in association with the abnormal gamma globulins of myelomatosis, including macroglobulinaemia, and also with cryoglobulinaemia in rheumatoid arthritis (Palm, 1947) and reticulohistiocytosis (Oglesby, 1961). Hobbs (1962) has summarized the various forms of morphological changes which have been observed. Crystalline changes affecting the anterior stroma have been described by Aronson and Shaw (1959), Bürki (1958), Palm (1947), and Pinkerton and Robertson (1969). When the posterior cornea has been affected, the changes have been of an amorphous nature (Oglesby, 1961), and the effect on vision has been significant.

Table III Summary of biochemical findings in nine cases compared with normal

Biochemical studies	Serum proteins (g/100 ml.)		Electrophoresis	Immunoglobulins (I.U./ml)				Hb (g. per cent.)	Erythrocyte sedimentation rate (mm/hr)	White blood cells (cells/mm ³)
	Albumin	Globulin		IgG	IgA	IgM	IgD			
Normal	4.4-5.4	1.8-3.2		Range 58-184 Mean 116	71-267 149	57-207 148	6			
Case no. 1	3.9	3.3	Raised gamma globulin	130	120	*225	4.7	12.9	17	10,000
2	4.3	2.2	Normal	88	64	82	0	13.5	14	diff. normal
3	4.3	3.1	Raised in gamma and alpha ² bands	160	257	165	6.0			8,000 diff. normal
4	4.2	2.7	Normal	—	Not carried out	—		15.3	12	5,000 normal
5	3.8	3.7	Raised gamma globulin	110	190	135	0			
6	4.0	3.7	Raised gamma globulin	*250	*235	92	*6.8	13.7	25	5,000 diff. normal
7	3.8	3.8		*200	115	82	11.5	14.5		8,000 diff. normal
8	Plasma cell myeloma-tosis			286	< 24	< 23				
9	— Not carried out —									

* Above the laboratory norm

In view of the disordered serum proteins in Case 8, and the known association between dysproteinaemia and corneal deposits (Hobbs, 1962), protein analyses were also carried out in seven of the other cases. The relationship between lattice dystrophy and the "light chain" deposits of amyloid led us to investigate the immunoglobulins in these patients.

Table III shows that the only consistent pattern that emerges is the relatively low serum albumin in every case compared to the laboratory norms. The significance of this is unknown. It does not appear to be nutritional, as other factors, particularly haemoglobin estimations, are within normal limits. Apart from Case 8, Cases 1, 3, 5, 6, and 7 show increased gamma globulins, though clearly the presence of normal readings in Cases 2 and 4 indicates that this is not an essential factor in the production of the corneal changes. König and Pur (1966) have described the occurrence of corneal amyloid in the presence of hypergammaglobulinaemia and it may be significant that their case also showed a reduced serum albumin. The immunoglobulin levels, though raised in the cases indicated, by the standard of the laboratory norm, do not show a consistent pattern which would suggest a specific immune disorder. Tests for specific tissue antibodies carried out in Cases 3 and 4 produced an antithyroid titre positive at 1:25,000 in Case 4,

but otherwise negative results to antinuclear, nucleolar, mitochondrial, gastric, smooth muscle, skeletal muscle, salivary duct, and neural antibodies. It was not felt worthwhile to pursue this aspect further in other patients at this stage.

The demonstration by Seitelberger and Nemetz (1961) and Klintworth (1967) that genetically-determined lattice dystrophy of the corneal stroma is a type of familial amyloidosis suggests the possibility that the condition described here is similar in view of morphological similarities.

The case reported by Strachan (1968) and an additional case observed by him (personal communication) appear to be identical to the cases reported here. It would seem inappropriate to include the disorder among the pre-Descemet's disorders, since the whole of the stromal thickness may be affected. The relationship between this condition and that described by Pillat (1939) is not clear.

It is suggested that the term "polymorphic stromal dystrophy" be adopted for this disorder.

Thanks are due to Mr. Dermot Pierse, Mr. M. Ruben, Mr. R. J. Strong, and Mr. D. Ainslie for permission to report their patients, and to Mr. T. Tarrant and members of the Department of Audio-Visual Communications for preparation of the illustrative material. We are grateful to Miss Elizabeth Evans for secretarial assistance.

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