Brit. J. Ophthal. (1966) **50**, 57

COMMUNICATIONS

MACULAR DYSTROPHY OF THE CORNEA*

BY

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THIS uncommon, disabling disease is characterized by an autosomal recessive inheritance, the presence of irregular corneal opacities with indistinct borders, and diffuse cloudiness of the stroma between the opacities (Fig. 1). Although the axial portion of the cornea is most severely affected the periphery shows opacities and the whole thickness of the substantia propria is usually involved. Macular dystrophy begins in childhood and there is rapid deterioration of vision.

In 1890, Groenouw reported two cases of nodular corneal dystrophy, and in 1938 Bücklers published a study of the hereditary corneal dystrophies which occurred in twelve family trees, and showed that there were two types of Groenouw's nodular dystrophy—a granular form which was inherited as a Mendelian dominant and a macular variety associated with recessive inheritance. In 1902, Fuchs had described the histological features of macular dystrophy for the first time, and during the past 25 years cases have been reported by a number of authors (e.g., Nastri, 1937; Bourquin, 1938; Bürki, 1939; Saebø, 1940; Mazzoletti, 1941; Fujikawa, 1942; Amsler, Dufour, and Hermann, 1943; Friede, 1943; Leffertstra, 1944; Sautter, 1944; Blum, 1945; Franceschetti and Babel, 1945; Sezer, 1946; Visser, 1948; Trovati, 1948; Van Canneyt and Kluyskens, 1948; Etienne, 1949; Kanter, 1949; da Silva, 1949; Jutrisa-Korinek, 1949; François, 1952; Jones and Zimmerman, 1959, 1961; Klintworth and Vogel, 1964). Consanguinity of the parents has been noted by Franceschetti and Streiff (1940), Blum (1945), Sezer (1946), and Moro and Amidei (1957).

Franceschetti and Babel (1945) consider macular dystrophy to be an intracellular process, but others feel that it is due to a degeneration of collagen fibres (Jones and Zimmerman, 1959, 1961). Recent work by Klintworth and Vogel (1964) has shown that the condition is an intracellular storage disease, the fundamental nature of which remains uncertain.

The purpose of this article is to present the clinico-pathological features of 13 cases of the condition seen at the Institute of Ophthalmology, London, and to describe the electron-microscopical changes and chromosome studies of one of them.

Findings

The clinical features are summarized in Table I. It will be seen that the dystrophy, which was bilateral in every case, started between early childhood and the age of 25 years. There was no evidence of consanguinity, and a family history was obtained in 8 of the 13 cases.

* Received for publication February 26, 1965.

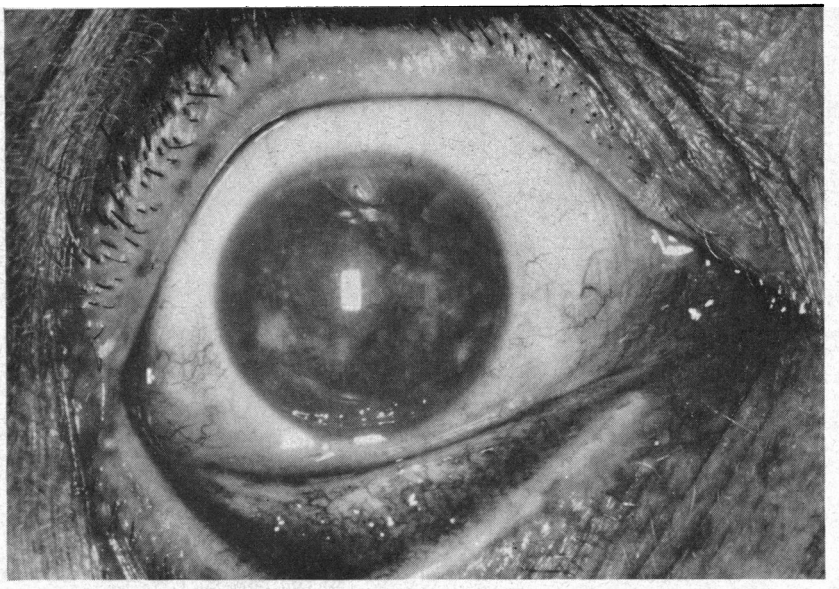

FIG. 1.—Clinical photograph of cornea, showing irregular opacities with indistinct borders, most marked axially, the opacities being separated by a cloudy stroma.

TABLE I

CLINICAL FEATURES OF 13 CASES OF MACULAR DYSTROPHY

Case	Sex	Age of Onset (yrs)	Unilateral or Bilateral	Consanguinity of Parents	Family History of Macular Dystrophy
1	F	16	Bilateral	No	1 Brother
2	F	12	Bilateral	No	No
3	M	25	Bilateral	No	No
4	M	10	Bilateral	No	No
5	F	20	Bilateral	No	1 Sister
6	M	Childhood	Bilateral	No	No
7	M	Childhood	Bilateral	No	No
8	M	6	Bilateral	No	1 Sister
9	M	Early childhood	Bilateral	No	1 Sister
10	F	Early childhood	Bilateral	No	1 Brother
11	M	Childhood	Bilateral	No	Maternal grandmother
12	F	Childhood	Bilateral	No	1 Brother
13	F	25	Bilateral	No	1 Sister

TABLE II

HISTOPATHOLOGICAL FEATURES OF 13 CORNEAL DISCS FROM PATIENTS WITH MACULAR DYSTROPHY

Case	Epithelium	Bowman's Membrane	Substantia Propria	Descemet's Membrane	Endothelium
1. Lamellar disc	Marked irregularity in thickness	Deficient	Number of corpuscles diminished; occasional superficial corpuscles showed abnormal material in the cytoplasm; abnormal material in superficial stroma		
2. Full-thickness disc	Marked irregularity in thickness	Deficient	Number of corpuscles normal; abnormal material in cells at all levels and in the superficial stroma	Normal	Abnormal material in endothelial cells
3. Lamellar disc	Marked irregularity in thickness	Deficient	Number of corpuscles diminished; abnormal material in cells at all levels and in the superficial stroma		
4. Lamellar disc	Marked irregularity in thickness	Deficient	Number of corpuscles normal; abnormal material in cells at all levels and in the superficial stroma		
5. Full-thickness disc	Irregular; absent in places	Deficient	Number of corpuscles diminished; abnormal material in cells at all levels and in the superficial stroma	Thickened	Normal
6. Full-thickness disc	Irregular in thickness	Thickened	Number of corpuscles diminished; abnormal material in cells and the stroma at all levels	Guttate swellings	Abnormal material in endothelial cells
7. Full-thickness disc	Irregular; absent in places	Deficient	Number of corpuscles diminished; abnormal material in cells at all levels and in the superficial stroma	Guttate swellings	Abnormal material in endothelial cells
8. Lamellar disc	Irregular; absent in places	Absent	Number of corpuscles diminished; some cells superficially and the superficial stroma contained abnormal material; superadded chronic inflammatory changes present		
9. Full-thickness disc	Irregular in thickness	Deficient	Number of corpuscles normal; abnormal material in cells at all levels and in the superficial stroma	Thickened	Abnormal material in endothelial cells
10. Full-thickness disc	Irregular in thickness	Irregular in thickness	Number of corpuscles normal; abnormal material in cells at all levels and in the superficial stroma	Thickened	Abnormal material in endothelial cells
11. Full-thickness disc	Irregular in thickness	Irregular in thickness	Number of corpuscles normal; abnormal material in cells at all levels and in the superficial stroma	Thickened	Abnormal material in endothelial cells
12. Lamellar disc	Irregular in thickness	Deficient	Number of corpuscles diminished; abnormal material in an occasional superficial cell and in the superficial stroma		
13. Full-thickness disc	Irregular in thickness	Deficient	Number of corpuscles normal; abnormal material in cells at all levels and in the superficial stroma	Guttate swellings	Abnormal material in endothelial cells

Histological examination showed the characteristic features of the condition. Mucoid material was deposited in the cytoplasm of the corneal corpuscles and in the collagen fibres, especially those of the superficial stroma. It will be seen in Table II that the number of corneal cells was diminished in 7 of the 13 eyes and normal in the other 6. Abnormal material, which stained positively with periodic-acid–Schiff (P.A.S.), alcian blue, toluidine blue, and colloidal iron stains, was found in the

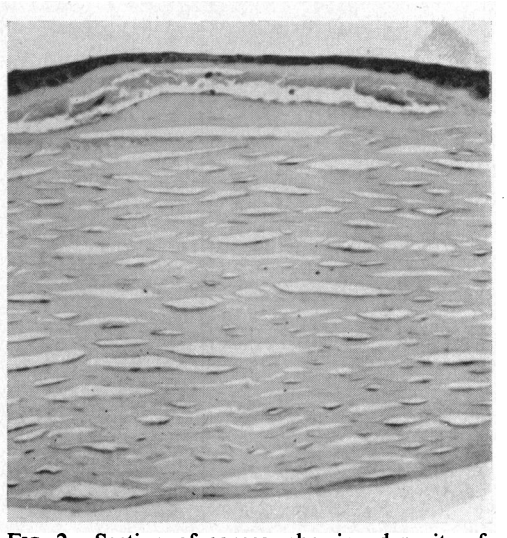

FIG. 2.—Section of cornea, showing deposits of abnormal material in the superficial stroma, which contain nuclear remnants. Bowman's membrane and the epithelium are thinned. Haematoxylin and eosin. × 116.

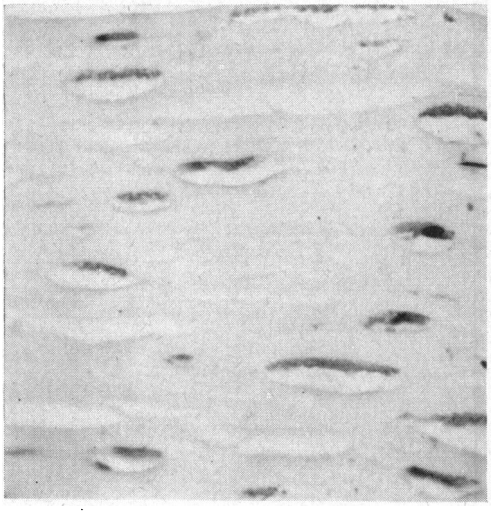

FIG. 3.—Section of cornea, showing deposits of abnormal material between the lamellae. Note the nuclear remnants in three of the deposits. Haematoxylin and eosin. × 390.

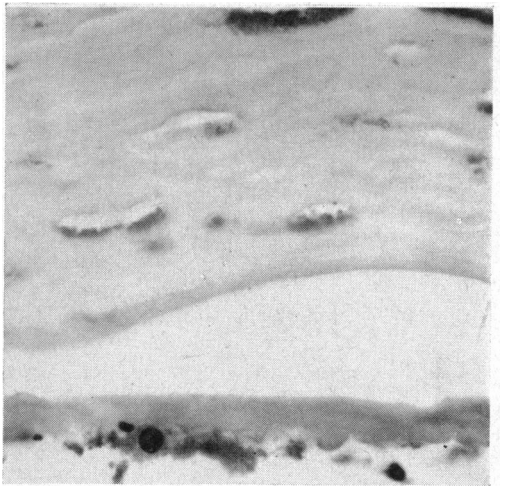

FIG. 4.—Section of cornea, showing stromal deposits and deposits within endothelial cells. Descemet's membrane is thickened and shows guttate swellings. Alcian blue. × 390.

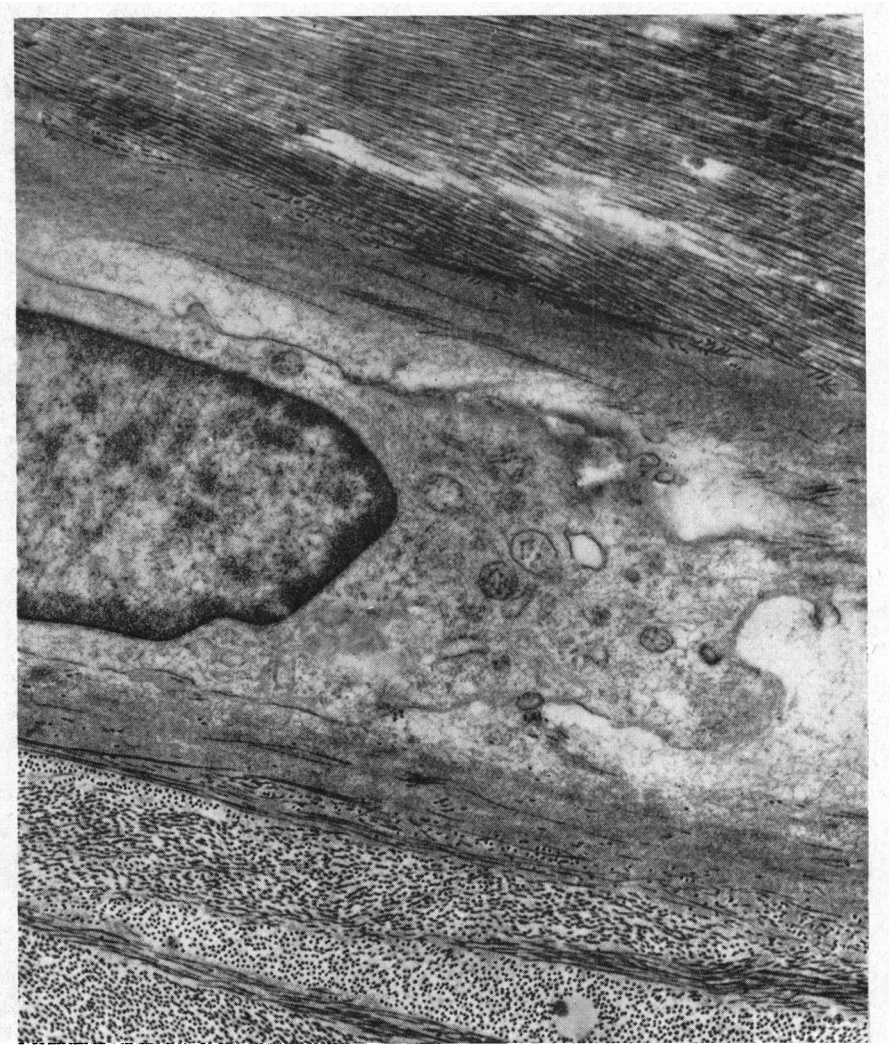

FIG. 5.—Electron-microscopical section, showing a corneal fibroblast in which the nucleus is normal. Electron-lucent material is present within its cytoplasm and outside the cell membrane. The collagen fibres are normal in appearance. × 18,000.

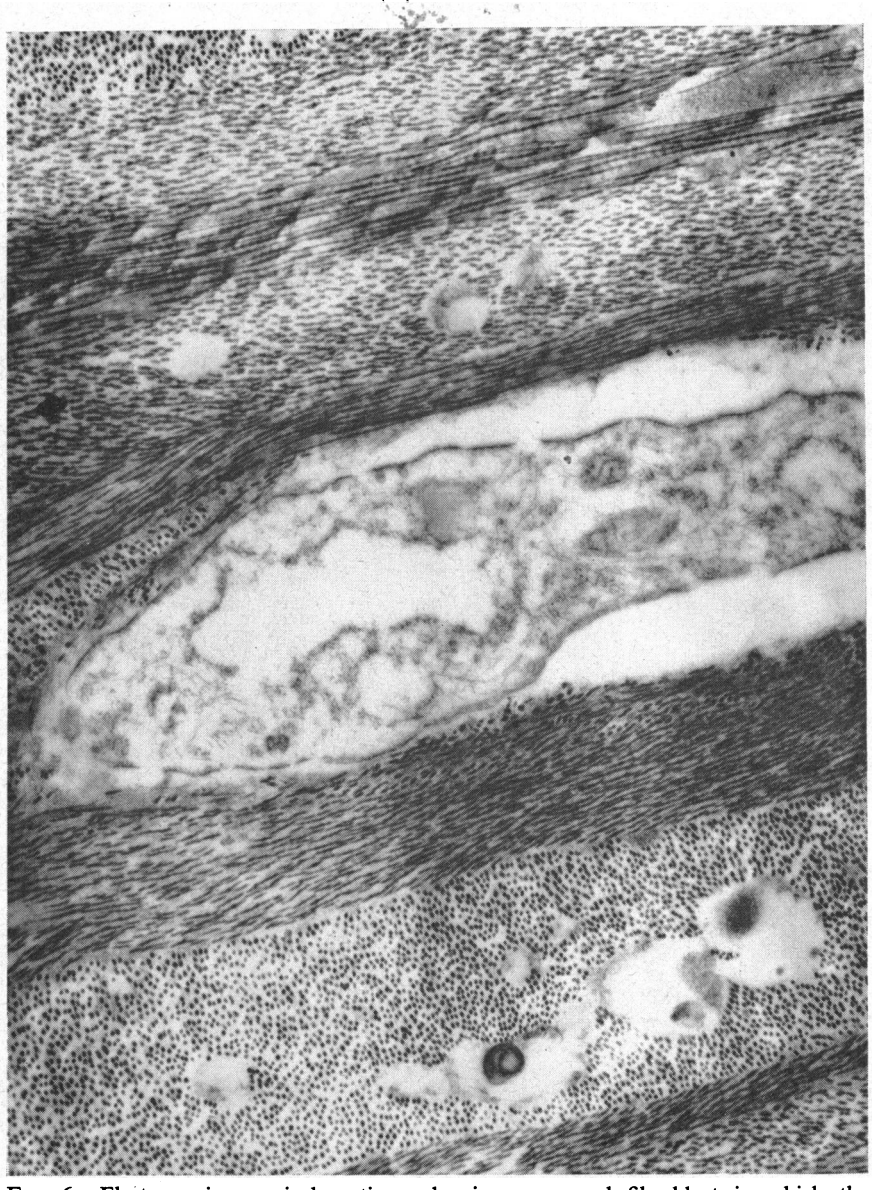

FIG. 6.—Electron-microscopical section, showing a corneal fibroblast in which the nucleus is not seen. The endoplasmic reticular canals are markedly dilated and contain small quantities of electron-lucent material which is also present in the cytoplasm. There appear to be several breaks in the cell membrane, and the material is present within vacuoles between normal collagen fibres. × 20,250.

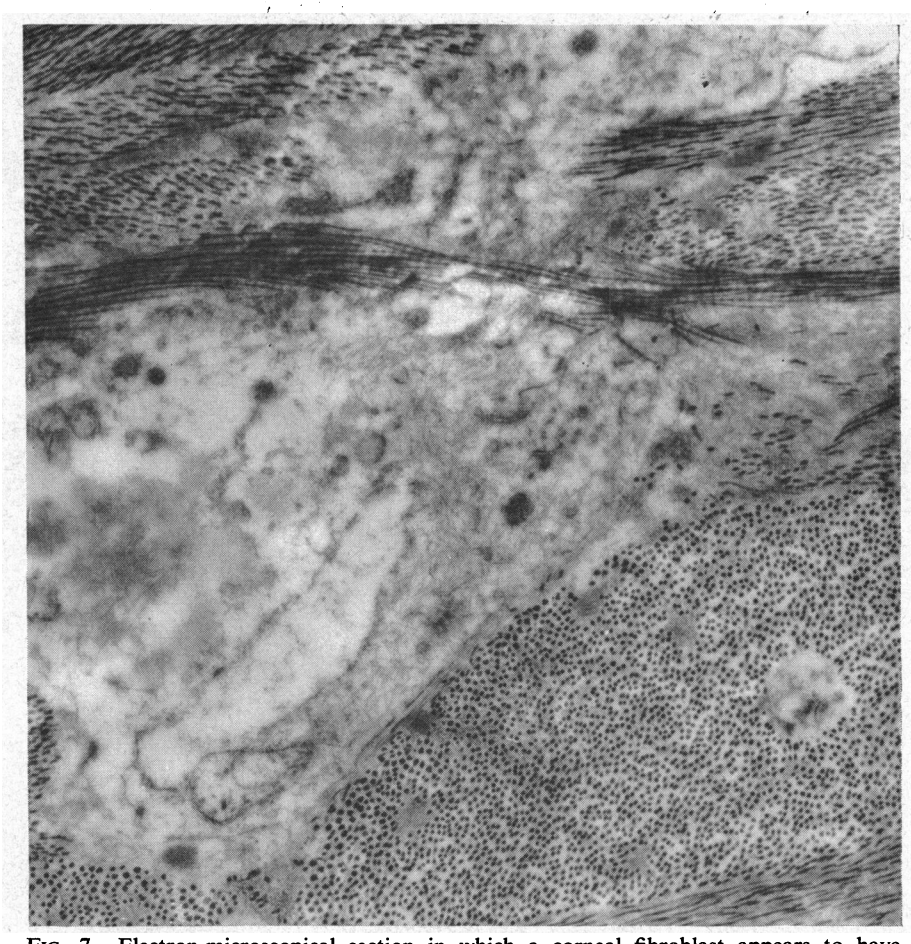

FIG. 7.—Electron-microscopical section in which a corneal fibroblast appears to have disintegrated, leaving a markedly dilated endoplasmic reticular canal which contains electron-lucent material similar to that which is present external to it and between the normal collagen fibres. × 20,250.

cytoplasm of the corneal cells, at all levels in 10 eyes and superficially in three. Deposits were seen in the superficial stroma in 12 eyes and at all levels in one (Figs 2 and 3), and in the endothelial cells of 7 out of 8 full-thickness corneal discs. The corneal epithelium, which was irregular in every eye, was absent in places in 3. Bowman's membrane was deficient in 9 eyes, absent in one, and irregular in thickness in 3. Descemet's membrane was thickened in 7 out of 8 discs, guttate swellings being seen in 3 of these (Fig. 4).

Electron microscopy was carried out in Case 5, part of the fresh corneal disc being fixed in 1 per cent. buffered osmium tetroxide. Sections showed the presence of large and small vacuoles within the cytoplasm of the corneal cells, and there is no doubt that some are dilatations of the endoplasmic reticular canals, for ribonuclear protein granules can be seen at the periphery. Abnormal electron-lucent material was seen within some of these vacuoles, in the cytoplasm, outside the cell wall, and between collagen fibres in the stroma (Figs 5 to 9). In places, it would appear

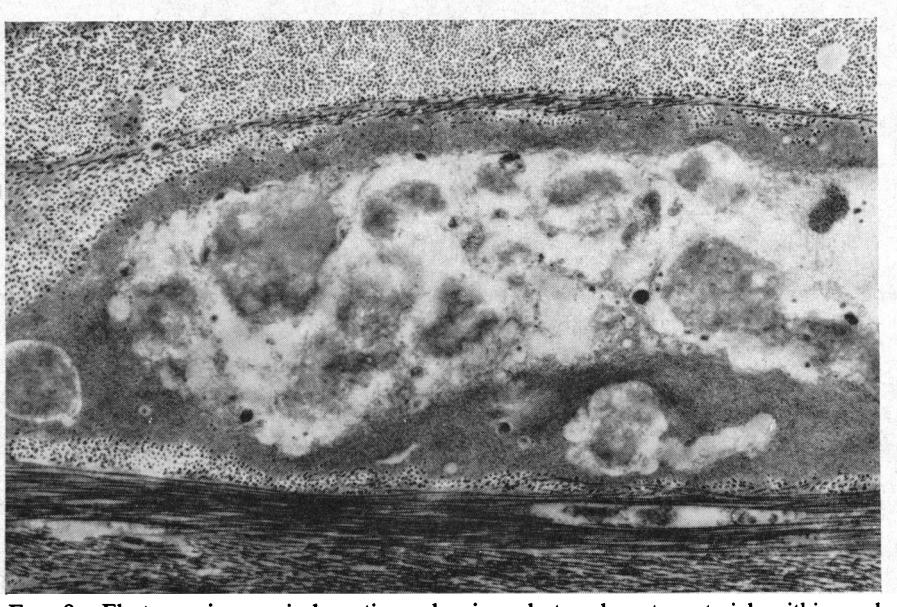

FIG. 8.—Electron-microscopical section, showing electron-lucent material within and outside vacuoles. × 15,000.

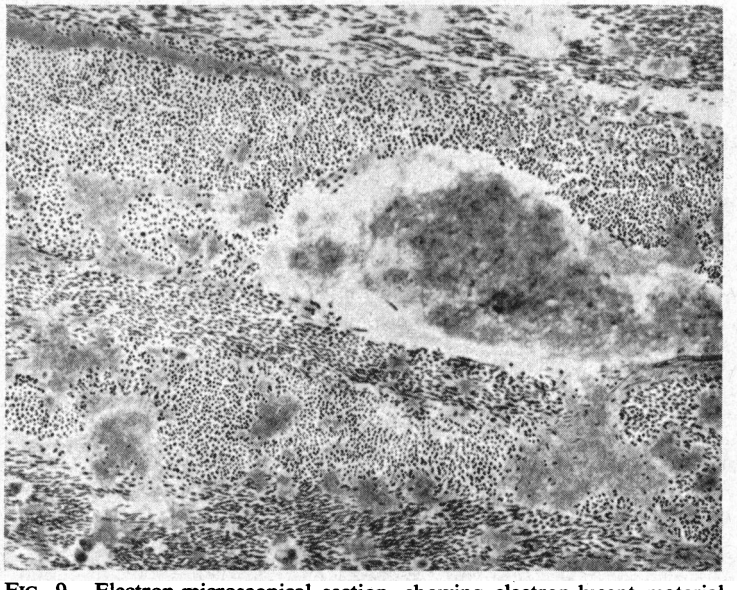

FIG. 9.—Electron-microscopical section, showing electron-lucent material deposits between normal collagen fibres. × 10,800.

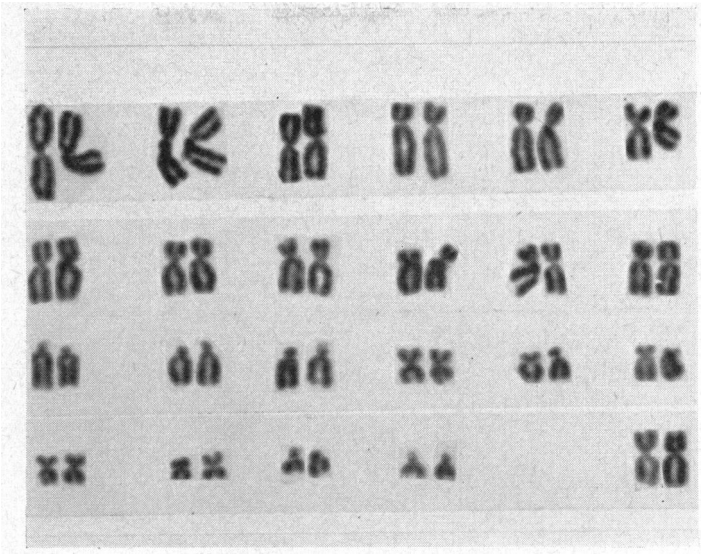

FIG. 10.—Normal karyotype for Case 5.

that the wall of some of the corneal cells was incomplete (Fig. 6), and the electron-lucent material had accumulated outside the cell. The collagen fibres did not show any evidence of degenerative change. Chromosome studies in Case 5 revealed a normal karyotype (Fig. 10).

Discussion

It would appear that the abnormal material which is deposited in the cornea in macular dystrophy is an acid mucopolysaccharide (Klintworth and Vogel, 1964). Staining of the material by P.A.S. demonstrates a 1, 2 glycol linkage (Pearse, 1960), by alcian blue a salt linkage between the alkaline groups of the dye and the acid of the substrate (Steedman, 1950), and metachromatic staining with dyes such as toluidine blue and crystal violet appears to depend upon a significant density of free electron-negative groups which attract the polar cationic groups of the dye (Pearse, 1960). The most specific stain for the material is probably colloidal iron, which depends on the binding of ferric iron to acidic groups at a low *p*H, a reaction made visible by the staining of the bound iron. Diverse compounds such as hyaluronic acids, sulphated mucopolysaccharides, nucleoproteins, esters of phosphoric acids, and like proteins are visibly demonstrated (Wigglesworth, 1952). These histochemical staining reactions characterize the material as an acidic molecule with an affinity for iron, having 1, 2 glycol, carboxyl, and possibly sulphate groups. It is stained, therefore, by techniques which yield positive reactions with acid mucopolysaccharides (i.e., P.A.S., alcian blue, metachromatic dyes, and colloidal iron).

The stromal cells of the cornea should be designated fibroblasts because they have been shown to synthesize collagen (Schwarz, 1961). Moreover, it is well known that connective tissue fibroblasts are able to form acid mucopolysaccharides, and it

seems reasonable to assume that in macular dystrophy of the cornea, there is an excessive production of acid mucopolysaccharide. This would lead to distension of the endoplasmic reticular canals, increased pressure within the cells, and rupture of the cell membrane with diffusion of the material into the stroma. The fact that diffusion can occur is supported by the accumulation of the material within the endothelial cells in some cases. The possibility that the disease may be a primary degeneration of the collagen fibres is not supported by the electron-microscopical appearances in Case 5 in which the collagen fibres appeared normal. If collagen degeneration is the primary abnormality, then the material would have to diffuse into the stromal cells. Although it is probable that diffusion could occur, the apparent breaks in the cell membrane are more likely to be associated with a primary cellular abnormality. Moreover, the diffusion of material through the cell membrane into the endoplasmic reticulum would invoke the fresh concept that these cytoplasmic structures have macrophagic properties. Although primary collagen degeneration is a possibility it seems much more likely that macular dystrophy of the cornea is primarily a cellular disorder.

I should like to thank Prof. Norman Ashton for his advice, and I am grateful to Miss E. Fitzgerald for secretarial help, and to Mr. F. H. Vincer, Mr. D. Wood, and Mr. V. J. Elwood for their technical assistance.

ADDENDUM

Since this article was written I have examined the corneal disc used for a keratoplasty which was carried out three years previously for macular dystrophy, and in which opacities had become apparent. Histological sections showed the typical features of this condition; the presence of acid mucopolysaccharide within the corneal fibroblasts, which had obviously grown into the graft from the periphery, is strong supporting evidence in favour of this condition being a cellular disorder.

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