NORTH CAROLINA MACULAR DYSTROPHY: CLINICOPATHOLOGIC CORRELATION*

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ABSTRACT

Purpose: To describe the clinical and histopathologic findings in a 72-year-old woman with North Carolina macular dystrophy.

Methods: Clinical examination was performed by slit-lamp biomicroscopy, indirect ophthalmoscopy, color fundus photography, and focal electroretinography. Histopathologic examination of the enucleated left eye consisted of light microscopy.

Results: Light microscopy demonstrated a discrete macular lesion characterized by focal absence of photoreceptor cells and retinal pigment epithelium. Bruch's membrane was attenuated in the center of the lesion and associated with marked atrophy of the choriocapillaris. Adjacent to the central lesion, some lipofuscin was identified in the retinal pigment epithelium.

Conclusions: North Carolina macular dystrophy has both clinical and microscopic appearances of a well-demarcated retinal and pigment epithelial lesion confined to the macula. This is consistent with the clinical impression that it is a focal macular dystrophy.

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INTRODUCTION

North Carolina macular dystrophy was the first macular dystrophy to be reliably mapped on the human genome (MCDR1).[1] This autosomal dominant macular dystrophy was first described in families living in the mountains of North Carolina. Subsequently, it has been reported in many unrelated families from the United States, United Kingdom, France, Germany, and Belize.[1-3] There is great phenotypic variability, with fundus appearances ranging from a few yellow drusen-like lesions less than 50 mm in the central macula (grade 1) to larger confluent lesions (grade 2) and macular staphyloma (grade 3).[1] The disease is generally stable, except in those who develop choroidal neovascular membranes. We report the first clinicopathologic correlation of a subject (No. 1001) from a Caucasian family (No. 1292) with MCDR1.[1] This family had no known genealogical relationship to the original North Carolina family (No. 765); however, they share the same affected haplotype on chromosome 6q16 and therefore are part of the original North Carolina macular dystrophy family.[1]

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CASE REPORT

At the initial examination in her home performed by K.W.S. in 1988, the 62-year-old patient was found to have bilateral macular scars with a best-corrected visual acuity of 20/40 in the right eye and 20/20 in the left eye. Institutional review board–approved consent forms were signed before the examinations. She stated that she had had decreased visual acuity since the age of 21 years and in about 1980 had "a bleed" in both eyes. Visual function spontaneously recovered in the left eye, but the right eye had residual metamorphopsia.

In 1990, she was examined again by K.W.S. at her residence. Best-corrected visual acuity at near had decreased to 20/100 in the right eye and 20/40 in the left eye. Color vision testing with Ishihara plates (Kanehara & Co, Ltd, Tokyo, Japan) was grossly abnormal with the patient missing 7 of 14 in the right eye and 5 of 14 in the left eye. Color fundus photographs taken with a handheld KOWA camera documented the disease as grade 2 bilaterally (Fig 1). There was a small area of apparent atrophy with some scarring at the central macula and drusen in the periphery. Focal electroretinograms (ERGs) were performed with the Doran maculoscope (Wortham, Mass). Results were

within normal range (0.182 μV amplitude, 37.4 msec implicit time foveal ERG right eye; 0.209 μV amplitude, 35.8 msec implicit time parafoveal ERG right eye; 0.172 μV/36.5 msec foveal ERG left eye; 0.108 μV/34.9 msec parafoveal ERG left eye).

At a subsequent examination in the subject's home in 1995, visual acuity in the right eye had improved to 20/70; acuity in the left eye was stable at 20/30 with the patient using a near vision card and wearing bifocals. At this visit, the macular lesions were unchanged at grade 2 severity. The subject died of a malignant astrocytoma in 2000.

MATERIALS AND METHODS

The patient's eyes were enucleated 2 hours after death. The left eye was fixed in a buffered formaldehyde and glutaraldehyde solution, and the right eye was frozen in liquid nitrogen for future studies shortly after enucleation. The left eye was opened in a horizontal plane above the optic nerve. A large segment containing the optic nerve head and macular lesion was processed in routine fashion for light microscopy. Four hundred serial sections were prepared and stained with hematoxylin and eosin and periodic acid–Schiff stains.

RESULTS

GROSS PATHOLOGY

No gross abnormalities in size, structure of the anterior segment, or optic nerve were noted. The fundus appearance correlated with the previously taken photographs: a small area of apparent atrophy with some scarring at the central macula bilaterally and drusen in the periphery (Fig 2).

LIGHT MICROSCOPY

Examination with light microscopy showed a discrete lesion in the fovea characterized by the abrupt transition from relatively normal macula to complete absence of photoreceptor cells and the underlying retinal pigment epithelium (RPE) (Figs 3A, 3B, 4). We did not document any evidence of choroidal neovascularization. Adjacent to the foveal lesion there was intercapillary pillar thickening of the choriocapillaris (Fig 5). Some accumulation of lipofuscin was identified within the RPE immediately bordering the lesion but not in the periphery (Fig 5). Occasional glial cells and pigmented macrophages were interposed between Bruch's membrane and the outer plexiform layer. Rare plasma cells and eosinophils were present. Central in the lesion, Bruch's membrane was severely attenuated and focally absent. The choriocapillaris was atrophic (Fig 6). Drusen were present throughout the eye but particularly abundant closest to the optic nerve and in the macula (Figs 7 and 8). Examination of the remainder of the posterior pole and periphery revealed only occasional drusen.

DISCUSSION

To date, the only macular dystrophies with histopathologic findings available for comparison to North Carolina macular dystrophy are Best's macular dystrophy,[4-6] fundus flavimaculatus with atrophic macular degeneration,[7-10] and adult-onset foveomacular pigment epithelial dystrophy (AOFPED).[12,13] The previous studies all included examination by light and electron microscopy. A common feature found in these diseases was prominent lipofuscin accumulation in the retinal pigment epithelium. Some studies also documented accumulation within the photoreceptors[5,10] and choroid.[4] This accumulation distended the RPE cells and caused great variability in size, up to 125 μm in diameter, with desquamation[7,8,10] or eventual rupture of contents into the subretinal space and apparent phagocytosis by pigment-laden macrophages and photoreceptors.[5-8,10] Similarly, we noted PAS–positive material consistent with lipofuscin in the macula of the patient described in the case report. The photoreceptor involvement in the studies varied from shortened outer segments[4,6,10] to complete degeneration, as was evident in our case.[5-7,10] Another notable finding in the macular dystrophies was choroidal neovascular membranes in Best's disease, which was absent on our case.[4-6] Curiously, we did find an anomalous retinal vessel in the outer nuclear layer in our case (Fig 8). Basal laminar and linear deposits were prominent in AOFPED.[12,13] Macular drusen and a discontinuous Bruch's membrane were observed in Best's disease as well as in our case.[4] Decreased ganglion cells were found in fundus flavimaculatus but not in our case.[10]

In our case as well as in the case of fundus flavimaculatus with atrophic macular degeneration reported by Eagle and associates,[7,11] there was replacement of the photoreceptors by presumed glial cells and choriocapillaris atrophy. However, unlike in our case, Bruch's membrane was normal in the case of fundus flavimaculatus. Lopez and colleagues[8] also found, in a case of autosomal dominant fundus flavimaculatus, an area of complete RPE and photoreceptor loss in the macula, similar to our case. The photoreceptor autolysis and RPE atrophy noted by Dubovy and associates[13] in a case of AOFPED, was surrounded by adjacent RPE cells distended by lipofuscin. Our findings show granular PAS-positive material consistent with lipofuscin surrounding the focal lesion but not distended. In the center of the lesion where the photoreceptors were absent, the retinal pigment epithelium was also absent and Bruch's membrane was irregular and discontinuous.

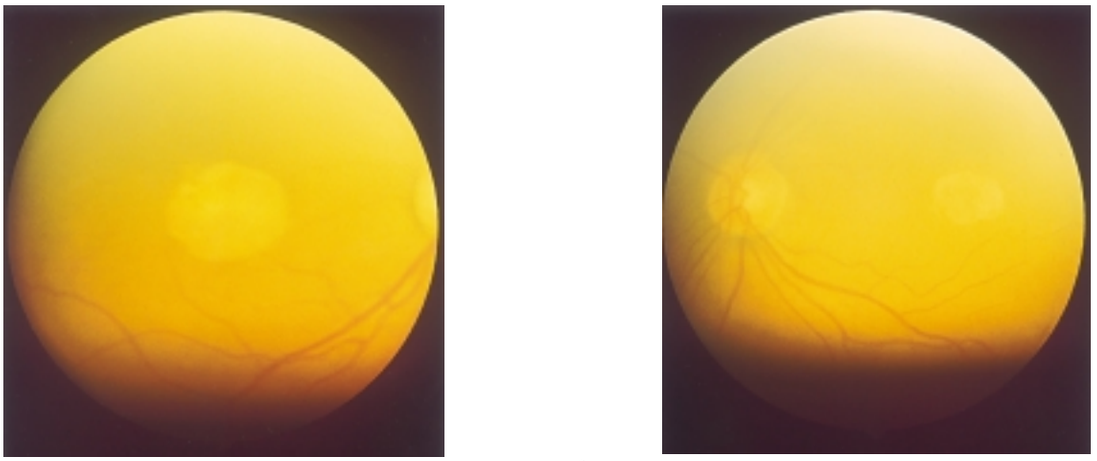

FIGURE 1
Fundus photographs of right (left) and left (right) eyes of subject described in case report, taken with a Kowa handheld camera in 1990

FIGURE 2
Gross photographs of left eye of subject described in case report, showing a focal macular lesion.

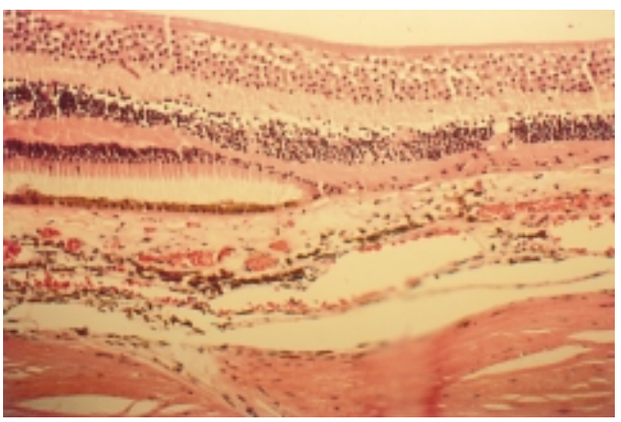

FIGURE 3A
Light microscopy showing abrupt transition from relatively normal macula to loss of photoreceptors and retinal pigment epithelium (hematoxylin and eosin, x 30).

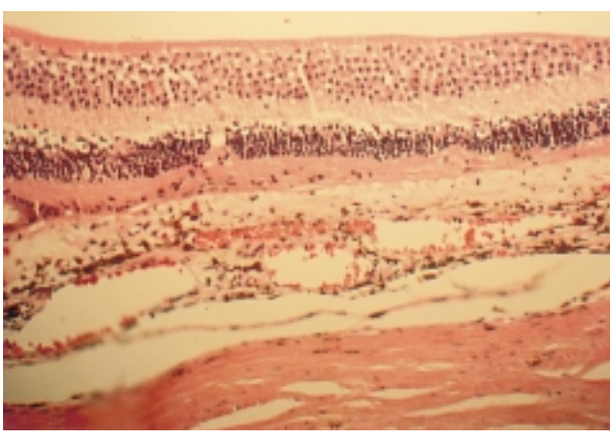

FIGURE 3B
Light microscopy showing foveal region and loss of photoreceptors (hematoxylin and eosin, x 30).

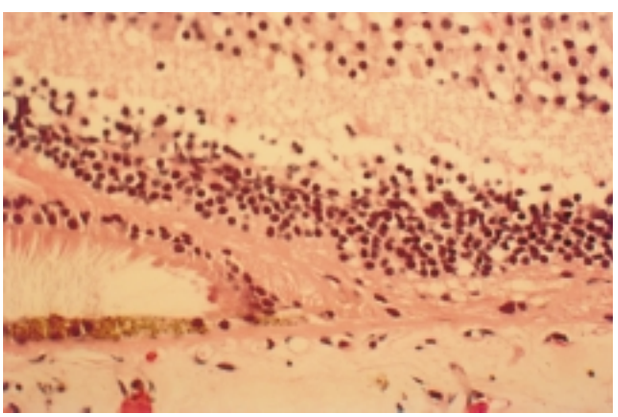

FIGURE 4
Light microscopy at higher magnification than in Fig 3, showing abrupt transition from relatively normal macula to loss of photoreceptors and retinal pigment epithelium (hematoxylin and eosin, x 125).

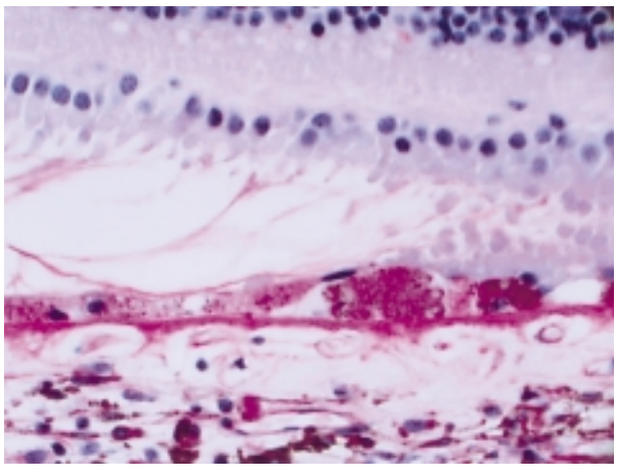

FIGURE 5
Retina adjacent to that shown in Fig 3. Note granular material positive for periodic acid–Schiff within retinal pigment epithelium and focal thickening of Bruch's membrane (periodic acid–Schiff, x 500).

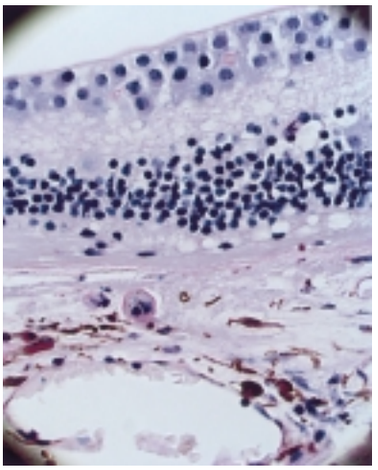

FIGURE 6
Photomicrograph showing marked thinning and apparent focal absence of Bruch's membrane. Choriocapillaris is atrophic (periodic acid–Schiff, x 500).

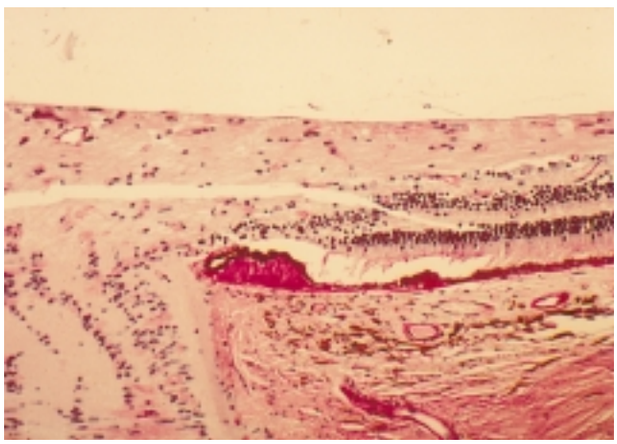

FIGURE 7
Photomicrograph showing large drusen and material positive for periodic acid–Schiff between Bruch's membrane and retinal pigment epithelium adjacent to optic nerve (periodic acid–Schiff, x 215).

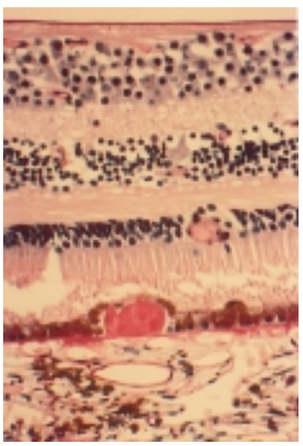

FIGURE 8
Photomicrograph showing large lobulated drusen in macula. Material positive for periodic acid–Schiff is interspersed between Bruch's membrane and vessels on choriocapillaris (periodic acid–Schiff, x 215).

The case of North Carolina macular dystrophy reported here most resembles that of AOFPED in that a discrete lesion involves only the central macula. The accumulation of lipofuscin within the retinal pigment epithelium adjacent to the lesion is characteristic of all cases of fundus flavimaculatus and Best's macular dystrophy and at least some cases of AOFPED. Drusen, as well as atrophy and fibrosis of the choriocapillaris, were present in the cases of AOFPED.

The case of North Carolina macular dystrophy presented here represents only one manifestation of a disease with highly variable expressivity. Therefore, additional histopathologic correlations will be needed to more fully understand this disease, and extrapolations from the findings of this single case should be made cautiously. Some of the cases of AOFPED have been related to a mutation in the peripherin gene. Further genetic studies are needed to identify the genetic abnormalities and pathogenesis of North Carolina macular dystrophy.

REFERENCES

1. Small KW. North Carolina macular dystrophy: Clinical features, genealogy, and genetic linkage analysis. *Trans Am Ophthalmol Soc* 1998;96:925-961.
2. Reichel MB, Kelsell RE, Fan J, et al. Phenotype of a British North Carolina macular dystrophy family linked to chromosome 6q. *Br J Ophthalmol* 1998;82:1162-1168.
3. Pauleikhoff D, Sauer CG, Muller CR, et al. Clinical and genetic evidence for North Carolina macular dystrophy in a German family. *Am J Ophthalmol* 1997;124:412-415.

4. Weingeist TA, Kobrin JL, Watzke RC. Histopathology of Best's macular dystrophy. *Arch Ophthalmol* 1982;100:1108-1114.
5. Frangieh GT, Green WR, Fine SL. A histopathologic study of Best's macular dystrophy. *Arch Ophthalmol* 1982;100:1115-1121.
6. O'Gorman S, Flaherty WA, Fishman GA, et al. Histopathologic findings in Best's vitelliform macular dystrophy. *Arch Ophthalmol* 1988;106:1261-1268.
7. Eagle RC, Lucier AC, Bernardino VB, et al. Retinal pigment epithelial abnormalities in fundus flavimaculatus: A light and electron microscopic study. *Ophthalmology* 1980;87:1189-1200.
8. Lopez PF, Maumenee IH, de la Cruz Z, et al. Autosomal-dominant fundus flavimaculatus: Clinicopathologic correlation. *Ophthalmology* 1990;97:798-809.
9. Steinmetz RL, Garner A, Maguire JI, et al. Histopathology of incipient fundus flavimaculatus. *Ophthalmology* 1991;98:953-956.
10. Birnbach CD, Jarvelainen M, Possin DE, et al. Histopathology and immunocytochemistry of the neurosensory retina in fundus flavimaculatus. *Ophthalmology* 1994;101:1211-1219.
11. McDonnell PJ, Kivlin JD, Maumenee IH, et al. Fundus flavimaculatus without maculopathy: A clinicopathologic study. *Ophthalmology* 1986;93:116-119.
12. Patrinely JR, Lewis RA, Forn RI. Foveomacular vitelliform dystrophy, adult type: A clinicopathological study including electron microscopic observations. *Ophthalmology* 1985;92:1712-1718.
13. Dubovy SR, Hairston RJ, Schatz H, et al. Adult-onset foveomacular pigment epithelial dystrophy: Clinicopathologic correlation of 3 cases. *Retina* 2000;20:638-649.

DISCUSSION

DR W. RICHARD GREEN. Dr Small and coworkers have provided a light microscopic evaluation of an eye of a person with the North Carolina macular dystrophy. Unfortunately, the authors found no clues to the understanding of the pathogenesis of the disorder. Whether or not there is an accumulation of lipofuscin in the RPE is insufficiently documented. Checking for autofluorescence and electron microscopy of the RPE adjacent to the area of atrophy would provide more documentation.

The partial atrophy of the photoreceptor cells at the margin of the area of atrophy where the RPE is relatively intact suggests that the primary defect may be in the photoreceptor cells rather than the RPE.

There is no question that variable scarring has been observed clinically in some cases of North Carolina Macular Dystrophy. In the study presented here, the authors describe the ophthalmoscopic appearance of "macular scars" and the gross appearance of "some scarring" in the central macula. The use of the term scar seems inappropriate in this case as no scarring is evident in the fundus photographs and none was observed histopathologically.

I would like to ask the authors if they attach any pathogenetic significance to the changes in the choriocapillaris that they described.

I would also like to ask Dr Small if he still believes that the North Carolina Macular Dystrophy and Central Areolar Pigment Epithelial Dystrophy are the same as he noted in the Archives of Ophthalmology, April, 1992. If that dystrophy is the same as central areolar choroidal sclerosis, then there have been numerous previous histopathologic studies - by Ferry, Eagle, Maumenee and Green. Carr observed a progressive intensity of disease in three generations. Ferry observed similar features as noted by Dr Small - loss of RPE and the photoreceptor cell layer and partial atrophy of the photoreceptor cell layer over intact RPE at the margin. Eagle documented the accumulation of lipofuscin by autofluorescence and we did the same by electron microscopy.

The authors do not indicate whether the subject of this study was a member of the pedigree(s) of North Carolina Dystrophy in which Dr Small reported genetic linkage analysis in his AOS thesis in 1998.

And finally, is the North Carolina Macular Dystrophy the same dystrophy reported in a North Carolina pedigree by Lefler, Wadsworth and Sidbury? Those authors, as well as Banks Anderson, observed an associated aminoaciduria. I ask Dr Small to clarify these points.

[Editor's note] DR RALPH C. EAGLE JR. commented that molecular biologic techniques will be required to understand North Carolina Macular Dystrophy. The histopathologic abnormalities in this case are non-specific, end-stage manifestations of macular degeneration.

DR KENT W. SMALL. I would like to thank Dr Green for his insights and for making his thoughts available to me prior to this meeting. This is a sign of a true gentleman and I appreciate his efforts. I will try to address his latter and simpler questions first, followed by attempting to address the more complicated issues.

First, how does this individual and family 1292, that we reported in this histopathologic case, relate genealogically to other published families with similar diseases? This family, 1292, is for all practical purposes a genealogic branch of the main large North Carolina Macular Dystrophy Family #765. Family 1292 had a branch that is from Western North Carolina and did descend from this area. Additionally, the disease associated haplotype on chromosome 6 is identical for families 1292 and 765, meaning North Carolina Macular Dystrophy Family for one in many centiMorgans around the locus. The probability of observing this by chance is smaller than 1 in a billion. Therefore, this individual reported today in this family is part of the same family described by Leffler, Wadsworth and Sidbury and Frank called hereditary macular degeneration and aminoaciduria. The aminoaciduria was subsequently determined to be a red herring and was published by Frank et al as dominant progressive foveal dystrophy. I have been able to document the relationship between these 2 families at the genealogical as well as the

molecular level. I also have extensive data, as shown in my AOS thesis, that the families of central areolar pigment epithelial dystrophy, described by Fetkenhour et al and Leveille et al, are indeed also the same phenotype as North Carolina Macular Dystrophy. From my experiences with North Carolina Macular Dystrophy, I feel strongly that "lumping" of phenotypes is far more appropriate than 'splitting." I would like to emphasize the need to study large numbers of affected individuals and large numbers of families in order to appreciate the full phenotypic variability of a disease. None of these family members, nor any subjects with central areolar pigment epithelial dystrophy, have been previously published histopathologically. The disease that Dr Green mentioned described by Carr, which has a middle age onset and is progressive, is actually described as central areolar choroidal dystrophy by Don Gass. This is a separate disease entity. Therefore, the case presented herein is indeed the very first histopathologic correlation of North Carolina Macular Dystrophy.

Now for the more complex issues, such as the pathogenesis and the significance of the changes in the choriocapillaris. I do not believe it is possible from histopathologic studies to determine if the focal absence of the choriocapillaris, as observed in our case, is the primary cause or a secondary effect from the absence of the retinal pigment epithelium. In my opinion, to attach pathogenic significance to this finding would be speculative at best.

I also agree with Dr Green and Dr Eagle that the term "scar" to describe the lesion in this subject is perhaps not as precise as we would like. There does appear to be "glial replacement" of the photoreceptors in a focal and discrete fashion, and this has been a finding that has been described as a "scar" by others in the past. This lesion in this patient does not appear to represent "confluent drusen" as I once believed, however.

I agree with Dr Green that the significance of the lipofuscin accumulation in the retinal pigment epithelium outside the macular lesion is unclear. We did demonstrate PAS positive material consistent with lipofuscin. Since graciously receiving Dr Green's comments, we have performed autofluorescent studies. Dr Glasgow feels that there is more autofluorescence in the posterior pole in our case compared to an age-matched control. The significance of this finding, however, still remains unclear. The retinal pigment epithelium normally autofluoresces and lipofuscin is a pigment found in the normal aging process. Even if there is a pathologic amount of lipofuscin, we still would not understand the pathogenesis of North Carolina Macular Dystrophy. Dr Flannery, one of my coauthors, did not feel that electron microscopy was important because the retinal pigment epithelium appeared normal to him outside the lesion.

For the really difficult issue: the pathogenesis of North Carolina Macular Dystrophy, also called MCDR1. I agree totally with Dr Green that our histopathologic study did not reveal any new clues to MCDR1, but I would not have expected a histopathologic study to reveal the pathogenesis of a genetic disease. We still do not know if MCDR1 is a disease primarily of photoreceptors, retinal pigment epithelium or choriocapillaris. Indeed, histopathologic studies of Stargardt's disease, fundus flavimaculatus, Best's disease and adult onset foveal macular pigment epithelial dystrophy were also incapable of precisely identifying which tissue was the site of primary disease and which tissue was secondarily affected. All of these diseases were previously thought to be primarily a retinal pigment epithelial disease until molecular genetic studies demonstrated that some are actually due to mutated proteins in the photoreceptors. Therefore, I maintain that clues to the pathogenesis of MCDR1 will only be discovered once the genetic defect is found. I predict that the gene is involved in the development of the macula since these lesions are congenital and fairly stationary throughout the life of the affected individual.

Again, I would like to thank the Society for this opportunity.

THESES