

## THE ATELIOTIC MACULA: A NEWLY RECOGNIZED DEVELOPMENTAL ANOMALY\*

BY *M. Elaine De Pool, MD* (BY INVITATION), *Hala El-Hileli, MD* (BY INVITATION), AND *Irene H. Maumenee, MD*

### ABSTRACT

**Purpose:** We present a macular phenotype resulting from 1 or more abnormalities in the developmental pathway of the central retina.

**Methods:** We describe the clinical and genetic characteristics of 7 patients observed since shortly after birth with regard to visual acuity, refractive error, anterior segment status, retinal findings including foveal structure, and natural history.

**Results:** The patients varied in age from 18 months to 18 years. All patients were examined for the first time during their first year of life and by us at the age of 5 years or younger. The longest follow-up period was 16 years. The abnormal appearance of the macula consisted of thinning of the retina, rarefaction of the pigment epithelium with excess visibility of the large choroidal vessels, and absence of the foveal reflex. The visual acuities varied from 20/20 in the better eye to light perception. A retinal detachment was noted in 1 patient at age 2 1/2 years. The refractive errors varied from -2.50 to -16.50 diopters of spherical equivalent. The disease was limited to the retina in 4 patients. In 2 patients, however, developmental abnormalities of the anterior segment were also present; they consisted of malformation of the iris in 1 patient and Peters' anomaly in the other. The electroretinogram (ERG) showed reduced but not absent photopic responses and some reduction in scotopic responses.

**Conclusion:** The phenotype of ateliotic macula is being defined as characterized by an unfinished or primordial appearance. In the 7 patients studied, visual loss was noted shortly after birth. The visual outcome was variable with regard to visual acuity, but many patients showed improvement. There was no evidence of significant worsening of the disease with age except in 1 patient who had a retinal detachment. The ERG responses showed primarily photopic but also scotopic changes. The better-preserved ERG differentiates this disorder from Leber's congenital amaurosis.

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### INTRODUCTION

For lack of better knowledge, we typically categorize genetic retinal diseases by their phenotype and not by their genotype. We may use mode of inheritance as a modifying descriptor. The term *ateliotic* means unfinished, not reaching the goal; this term was chosen because of the primordial appearance of the macula. Terms such as retinitis pigmentosa continue to be used for historical reasons, even though this term is obsolete because of the implied inflammatory etiology of the disease and the identification of significant heterogeneity. By definition, retinitis pigmentosa is a progressive disorder, in contrast to Leber's congenital amaurosis (LCA), which commonly is stationary but rarely may be progressive. In retinitis pigmentosa, rod function is primarily involved; in LCA, both cone and rod function are absent. The ateliotic macula is characterized by primarily cone dysfunction, which is congenital and stationary; some patients may show

significant visual improvement with time. The genetic defect(s) for this phenotype remain(s) unknown.

### METHODS

We studied 7 patients with regard to natural history, visual acuity, psychophysical testing, fundus appearance, and mode of inheritance. Visual fields, scanning laser ophthalmoscopy, Ocular Coherence Tomography (OCT), fluorescein angiography, and indocyanine green studies were performed in 1 older patient only.

### CASE 1

The patient was first examined at the age of 5 years. Visual acuity was 20/200 in each eye. Retinoscopic findings were -3.50 +1.25 x 85 and -3.75 +1.25 x 90. Pigmentary changes were seen in the macular area. The patient did not have nystagmus, but he had a red-green color defect. An electroretinogram (ERG) showed a normal scotopic response and a mildly reduced photopic b-wave. Funduscopy showed a staphyloma-like appear-

\*From The Johns Hopkins Center for Hereditary Eye Diseases, Baltimore, Maryland.

ance to the macular area and absence of macular reflex. The patient was last examined at the age of 17 years. At that time, visual acuities were 20/60 and 20/70 and retinoscopic findings were  $-2.25 +1.25 \times 60$  and  $-4.25 +1.00 \times 90$  (Figs 1A and 1B).

#### CASE 2

The patient was first examined shortly after birth, when she was given a diagnosis of Leber's congenital amaurosis. Results of an ERG performed by us were normal. The patient had a hypoplastic macular reflex in the right eye and an "ateliotic macula" on the left. Amblyopia therapy was instituted. At the age of 2 years her acuities were fix and follow in each eye with continued preference of fixation of the right eye. The appearance of the macula had not worsened in the left eye and was judged to be normal in the right (Figs 2A and 2B).

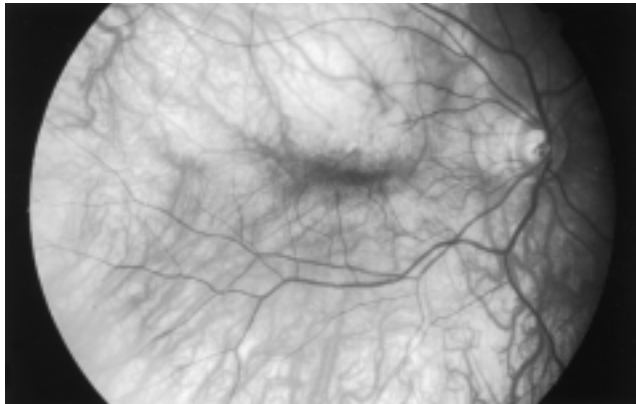
#### CASE 3

At examination at the age of 2 months, the patient would blink to light with both eyes. She had roving eye movements. Acuity was light perception only. We first exam-

ined the patient at age 11 months. Her fixation had become central and was not steady but maintained. There was a poor foveal reflex in each eye with pigment migration in the macular area and a dropout of normal structures in the peripheral retina temporal to fixation. Retinoscopic findings were  $-2.50$  and  $-11.50$ . When examined at 2 years of age, her visual acuity was 3/30 to the Allen cards in each eye. Refraction was  $-11.75 +1.75 \times 85$  and  $-13.00 +1.50 \times 85$ . Fundus evaluation showed continued coarse retinal pigment epithelial changes and a poor foveal reflex in each eye.

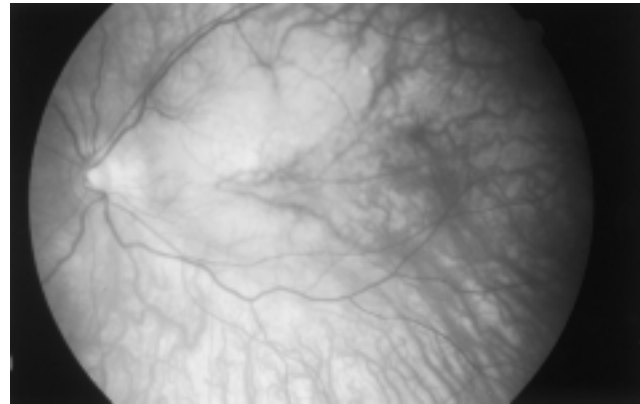
#### CASES 4 AND 5

These patients, the female children of healthy, first cousin Egyptian parents, were examined at  $2\frac{1}{2}$  and  $1\frac{1}{2}$  years of age on account of markedly reduced visual acuity since birth. The older sibling had a retinal detachment with a detached macula in the right eye. Refractive error in the left eye was  $-11.50$ . Bilateral atrophic patches were seen in the macular area. The patient underwent a retinal detachment procedure to the right eye. Her younger sister had nystagmus and bilateral atrophic patches in the



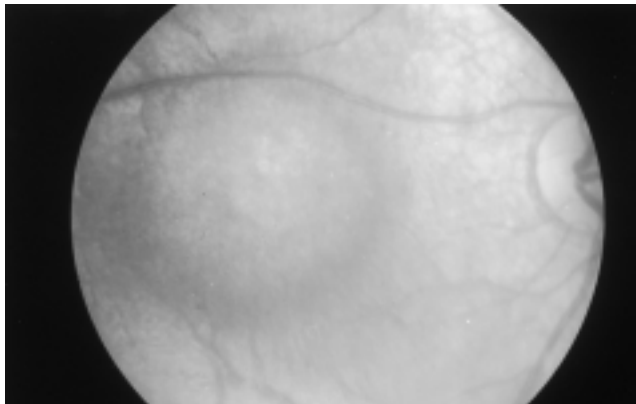
**FIGURE 1A**

Case 1. Right eye of patient with macular staphyloma OU.



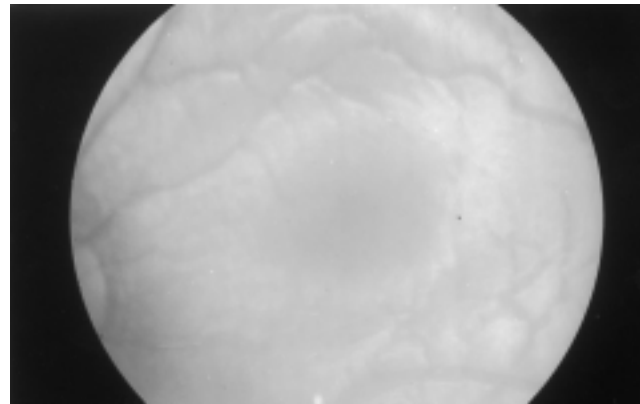
**FIGURE 1B**

Case 1. Left eye of patient with macular staphyloma OU.



**FIGURE 2A**

Case 2. Right eye of patient with asymmetric "ateliotic macula."



**FIGURE 2B**

Case 2. Left eye of patient with asymmetric "ateliotic macula."

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macular area. Retinoscopic findings were  $-13.50 +5.00 \times 110$  and  $-11.50 +2.00 \times 80$ .

#### **CASE 6**

At age 9 days the patient was noted to have a corneal opacity on the right. He underwent examination under anesthesia elsewhere. At that time, intraocular tension was normal in both eyes and no iridocorneal adhesions were noted. We began following the patient's clinical course when he was 3 weeks old. At 2 years of age, intraocular pressure increased and treatment with Timoptic was begun. Torch titers were negative, and a karyotype was normal. His gait was broad-based. He developed grand mal seizures, and a magnetic resonance imaging scan was performed. He was found to have hypoplasia of the cerebellar vermis, and a diagnosis of Joubert's syndrome was made. Refractive errors were  $-4.50 +5.00 \times 135$  and  $-14.50 +3.50 \times 175$ . He had macular changes on the right that showed a bull's-eye appearance with pigment migration. He had a pit of the right optic nerve, which was tilted. In the left eye, involvement of the macular area was more significant, with large areas of depigmentation and rarefaction and hypoplasia of small choroidal vessels. Electroretinography revealed scotopic and photopic responses. Visual acuities at age 3 years were 5/30 and 1/30 with Allen cards (Figs 3A, 3B, and 3C).

#### **CASE 7**

The patient was first examined at age 6 months, when he had central steady and maintained fixation in the right eye. There was no obvious nystagmus. The anterior segment on the right was normal, and an eccentric minute pupillary opening measuring less than 1 mm was present on the left. An optical iridectomy was performed. The patient had a mild hypermetropic refractive error with anisometropia. He had bilateral macular changes consisting of a bull's-eye appearance. He was lost to follow-up until the age of 18 years. At that time, his visual acuities measured 20/20 in the right eye and finger counting in the left. Retinoscopic findings were plano in the right eye and  $-11.50 +7.00 \times 130$  in the left. No improvement was seen on manifest refraction. A fluorescein angiogram on the right showed a bull's-eye maculopathy. Results of an indocyanine green study were normal in both eyes. Findings on scanning laser ophthalmoscopy and focal ERG were normal as well (Figs 4A, 4B, and 4C).

#### **RESULTS**

The age and sex of the 7 patients in the study population are summarized in Table I. All cases of ateliotic macula were bilateral with significant variation in severity of the disease in the 2 eyes. Disease was characterized by congenital

onset. The disease was stationary and did not show progressive degenerative changes; rather, a slow improvement in visual function was observed in most patients.

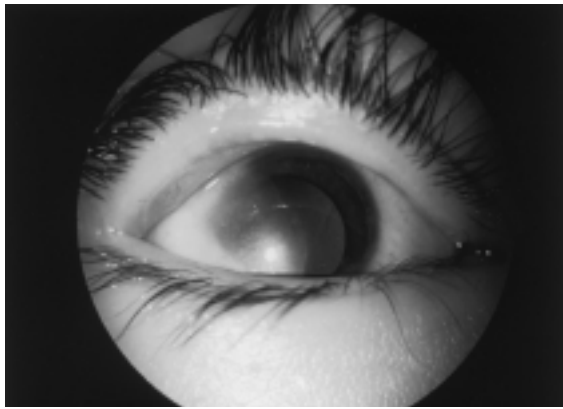
Visual acuity ranged from normal to light perception only. The macula was characterized by a bull's-eye appearance to diffuse atrophic changes involving the whole posterior pole. There was excess visibility of the choroidal pattern with atrophy of the choriocapillaris and mild pigment migration in several of the affected patients. Color vision was affected. The refractive errors showed mild to very high myopia; anisometropia was common. One patient with high myopia was observed to have a retinal detachment at age 2 1/2 years. In this patient, no findings were suggestive of the Stickler or Knobloch syndromes.

Collagen XVIII, the gene involved in the Knobloch syndrome, was studied in all patients. No abnormality was found. In 1 patient, fluorescein angiography showed a bull's-eye appearance in the right eye, with a visual acuity of 20/20, and diffuse pigment displacement in the fellow eye, with a visual acuity of light perception only. Results of scanning laser ophthalmoscopy were normal in the right eye in spite of the bull's-eye appearance. The retinal thickness was at the lower limit of normal. An ERG showed a low normal response to the photopic flicker in the eye with normal acuity and 1/3 normal response in the fellow eye, which also had a reduction in rod response.

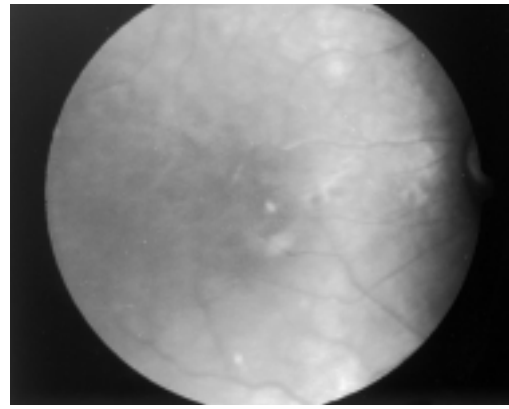
Patients showed a markedly reduced cone response and a variable reduction in rod response. Fundus appearance of the patients with high myopia was characterized by a disorganized macular area resembling the fundus appearance seen in patients with the Knobloch syndrome. There was a primordial appearance suggesting the term *ateliotic macula*. *Ateliotic* is derived from the Greek *telos*, meaning end or goal.

#### **DISCUSSION**

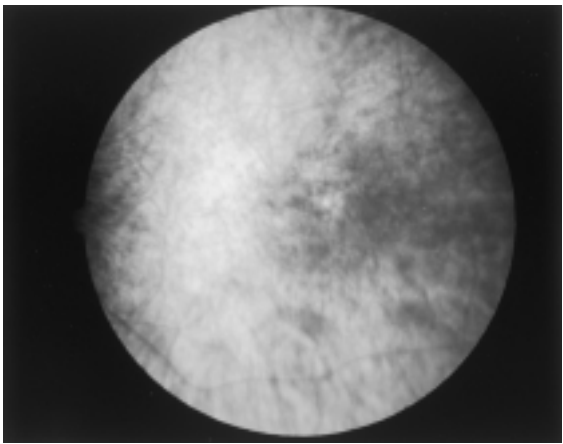
A large family with high myopia and a congenital macular anomaly was observed at St John's Hospital in Jerusalem by Iqbal and Jalili.<sup>1</sup> The parents were first cousins, and the mode of inheritance was clearly autosomal recessive. A similar, though smaller, family with recessive high myopia and macular changes is now being described by us. The family originated from Upper Egypt (patients 4 and 5). All other patients were identified and evaluated here in the United States. They were all isolated cases, and no definite identification of the mode of inheritance could be established. Both sexes were equally involved. Two patients had anterior segment malformations. The patient with unilateral partial corneal opacities had better retinal function in the affected eye. All patients had normal intelligence, and no other systemic abnormalities were noted except for 1 patient who had complex

**FIGURE 3A**

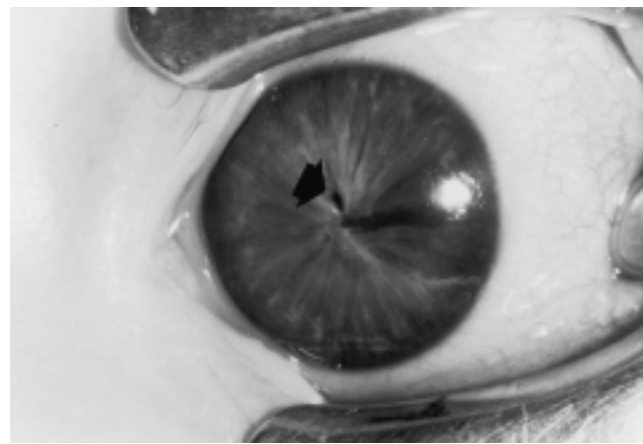
Case 6. Anterior segment with Peters' anomaly.

**FIGURE 3B**

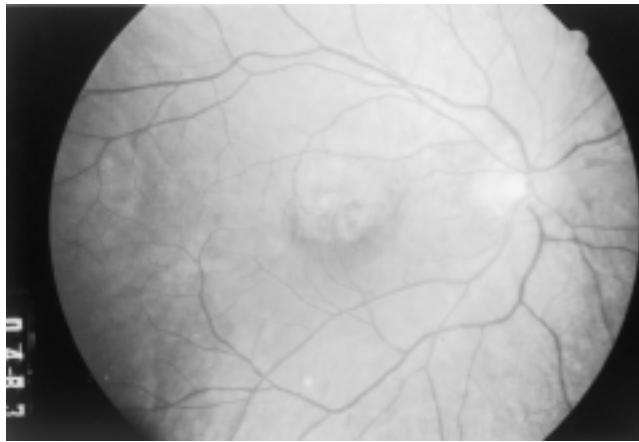
Case 6. Right macular hypoplasia.

**FIGURE 3C**

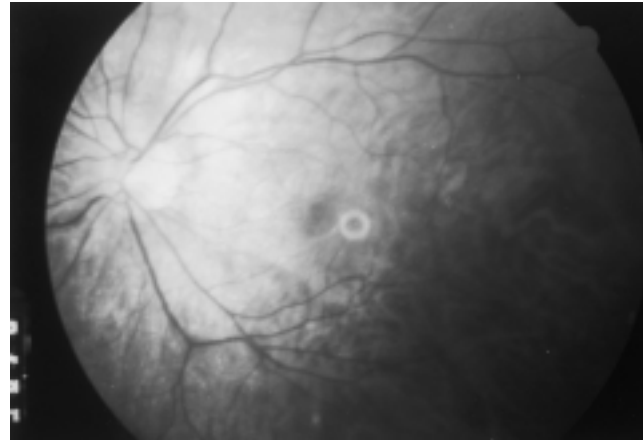
Case 6. Left macular pigment migration.

**FIGURE 4A**

Case 7. Left congenital malformation of the iris. Arrow indicates pupillary opening.

**FIGURE 4B**

Case 7. Right ateliotic macula with normal visual acuity.

**FIGURE 4C**

Case 7. Ill-defined macula with pigment migration and chorioretinal atrophy.

malformations including hypoplasia of the vermis and an unexplained seizure disorder.

A variable macular phenotype of congenital onset with early poor visual acuity and an amorphic appearance to the macula is described. Parents typically consult in multiple

centers without receiving diagnostic confirmation or prognostic assessment. Classification certainly should serve the purpose of defining unique prognostic entities. It should similarly define entities that will benefit from the same treatment approach. The classification of patients under the

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TABLE I:

PATIENT	AGE	SEX	ACUITY	REFRACTION	ANTERIOR SEGMENT	FUNDUS	ERG
1	17 yr	M	20/60	2.25+1.25 x 60 20/70	Normal	Macular lesions OU	Normal scotopic, mildly reduced photopic
2	7 mo	F	F&F OU Prefers OS	-1.50+1.50 x 65 -1.00+1.50 x 90	Normal	Macular pigment changes OD, ateliotic macula OS	Normal for age
3	3 yr	F	CSM OU	-1.75+1.75 x 85 -13.00+1.50 x 85	Normal	Poor foveal reflexes chorioretinal dropout lesions, temporal to fixation	Present scotopic and photopic responses OU
4	2 1/2 yr	F	Poor	OS -11.50 sph	Normal	Retinal Detachment OD; "colobomatous macula" OS	
5	1 1/2 yr	F	Poor	-13.50+5.00 x 1.10 -11.50+2.00 x 80	Normal	Abnormal macula, myopic fundus OU	
6	3 yr	M	5/30 Poor fixation	-6.50 -16.50	Peters' anomaly	Macular lesion OU	Decreased scotopic and photopic amplitudes
7	18 yr	M	20/20 LP	Plano -11.50+7.00 x 130	Microcoria s/p sx OS	Atrophic macular area OU	Decreased photopic amplitude OS

CSM,; F & F, fix and follow; LP, light perception.

heading of ateliotic macula appears justified because they are united by the observation that the visual outcome appears much better than originally anticipated. The subgroup of patients with high myopia had the most primordial-looking macula. Their prognosis was also worse because of the development of a retinal detachment. It is unclear whether ocular findings in patients are worsened by their myopia or whether a separate gene defect is responsible for the families' combining macular dysplasia and high myopia. The studies by Anita Hendrickson and coworkers<sup>2-4</sup> have shown that the retinal photoreceptors develop in a centrifugal fashion with the origin in the macular area.

The genes involved in development of the fovea remain largely unexplored. Mutations in the CRX gene are known to cause a congenital anomaly of the macula. This gene has not been analyzed in these patients. The large Palestinian family with autosomal recessive inheritance should prove sufficiently large for successful linkage analysis and gene search. All isolated patients are probably best analyzed once mutation-specific diagnostic microchip analysis is possible.

Certainly previously named conditions such as North Carolina macular degeneration, progressive bifocal chorioretinal dystrophy, and Sorsby syndrome<sup>5</sup> are in the pathway of development of the macula. Several patients seen here had features reminiscent of the Knobloch syndrome.<sup>6</sup> No mutations were found in sequencing of that gene.

Understanding of the genes involved in macular development may become essential to treatment of macular degeneration in the elderly. It seems justified to create a new term to define developmental disorders of

the macula, beyond "hypoplastic macula," which defines absence of fine modeling of the macula.

## CONCLUSION

The understanding of developmental anomalies of the macula is integral to the understanding of cone function for potential repair and treatment. Large pedigrees need to be identified in order to isolate the genes responsible for the developmental disorders. Many patients present as isolated cases, and the prognosis and risk for recurrence need to be assessed on an individual basis; once the genes have been identified, a more accurate mutation-based assessment will become possible.

## REFERENCES

1. Iqbal M, Jalili IK. Congenital-onset central chorioretinal dystrophy associated with high myopia. *Eye* 1998;12:260-265.
2. Sears S, Erickson A, Hendrickson A. The spatial and temporal expression of outer segment proteins during developmental of Macaca monkey cones. *Invest Ophthalmol Vis Sci* 2000;41(5):971-979.
3. Xiao M, Hendrickson A. Spatial and temporal expression of short, long/medium, or both opsins in human fetal cones. *J Comp Neurol* 2000;425(4):545-559.
4. Milam AH, Hendrickson AE, Xiao M, et al. Localization of tubby-like protein 1 in developing and adult human retinas. *Invest Ophthalmol Vis Sci* 2000;41(8):2352-2356.
5. Sorsby A. Congenital coloboma of the macula, together with an account of the familial occurrence of bilateral macular coloboma in association with apical dystrophy of hands and feet. *Br J Ophthalmol* 1935;19:65-87.
6. Cook GR, Knobloch WH. Autosomal recessive vitreoretinopathy and encephaloceles. *Am J Ophthalmol* 1982;94:18-25.

## DISCUSSION

DR C. P. WILKINSON. Drs Maumenee, De Pool, and El-Hileli have described 7 patients with apparent macular hypoplasia, myopia, and additional isolated findings. They have employed the term "ateliotic" to refer to the macular changes that were present in these cases. They have demonstrated that these eyes were not associated with genetic abnormalities characteristic of the Knobloch syndrome. It is difficult to know if the ERG changes are consistent with high myopia or if they are representative of more severe diffuse retinal disease.

The term "ateliotic" is defined in Dorland's medical dictionary<sup>1</sup> as: "characterized by incomplete or imperfect development." This term seems to me to be consistent with the terms "dysplastic" and "hypoplastic". Regardless of the precise wording that is employed, these macular changes are seen in a variety of syndromes, including systemic and ocular albinism, Knobloch syndrome, aniridia, PHPV, and incontinentia pigmenti. The findings also occur unassociated with apparent additional ocular or systemic problems. For instance, in 1976, Curran and Robb<sup>2</sup> described 9 patients with hypoplastic maculas and congenital nystagmus, and two-thirds of the patients were myopic. No additional problems were identified.

The Knobloch syndrome, named in honor of our own member, Bill Knobloch, was first described in 1971.<sup>3</sup> Subsequently, additional findings have been added to the syndrome, and most importantly, the site of the genetic defect has been identified.<sup>4</sup>

Regarding the 7 cases presented this morning, the precise category in which they belong is unclear. These obviously are not 7 examples of a similar macular morphology. Some appear to be similar to several of the cases described many years ago by Curran and Robb, whereas others do not appear to have classical hypoplasia of the macula, but rather changes ranging from apparent scarring at the level of the retinal pigment epithelium to an albinoid appearance.

I have 3 questions for the authors:

1. Why introduce the esoteric term "ateliotic" to replace the more widely used words "hypoplastic" or "dysplastic", when the latter terms have been used for decades in referring to typical macular changes?
2. Were major Sticklers-like vitreous changes observed in these cases? An optically-empty vitreous cavity transversed by bands and sheets is frequently seen in eyes predisposed to retinal detachment, and many of these patients have systemic disorders associated with collagen production.
3. Finally, why do the authors believe that these 7 patients are particularly predisposed to retinal detachment?

## REFERENCES

1. Dorland's Illustrated Medical Dictionary. 1981, Philadelphia, W. B. Saunders, p. 133.
2. Curran RE, Robb RM: Isolated foveal hypoplasia. *Arch Ophthalmol* 1976;94:48-50.
3. Knobloch W, Layer I: Retinal detachment and encephalocele. *J Pediatr Ophthalmol* 1971;8:181-184.
4. Sertie, AL, Quimby, M, Moreira, ES, et al: A gene which causes ocular alterations and occipital encephalocele (Knobloch syndrome) is mapped to 21q22.3. *Hum Mol Genet* 1996;5:843-847.

DR RICHARD A. LEWIS. I too was struck by the selection of the title and description of the "ateliotic macula", in part for the substitution of the more common "macular hypoplasia", in part for the adjectival prefix, and in part for the complexity of the admixture of Greek and Latin terms.

"Hypoplasia" is the fusion of the Greek preposition "υπο" ("hupo" or "hypo" meaning 'under' or 'less than') and the noun "πλασις" ("plasis", the root noun for 'molding', 'shaping' or 'conformation' [from which we derive 'plasma', 'plaster', and 'plastic'] and thereby 'growth'), thus "defective formation, or incomplete development of a part." Historically, hypoplasia has been applied to the failure to differentiate a normal fovea (ophthalmoscopically confined as the area of thickened retina confined by the elliptical foveal light reflex on the internal limiting membrane at the base of the slope of the thinning neuroepithelium and centered on the umbo), and classically associated with less than normal vision as in the albinisms, aniridia, and the like).

The macula is a larger ophthalmoscopic region confined by the major temporal vascular arcades, centered on the umbo, and extending temporally the same chord distance as in the umbo from the temporal edge of the sclerochoroidal rim. "Macula" is the Latin diminutive of "macus", meaning 'area' or 'spot'; thus "macula" is the 'little spot'.

"Ateliotic" is derived from the Greek adjective "τελος" ("telos"), meaning "far" [thus the prefix in common English words like 'telephone' and 'television']. "ατελης" ("ateles") (with the negative prefix "α", roughly the equivalent of our "un-") thus means "without end, unaccomplished, imperfect, or incomplete" and is the root for the scientific or medical term "atelirosis" (adjectival form: 'ateliotic'), meaning the "incomplete development of the body or any of its parts".

However, it may be unnecessary to invoke a compound term for this failure of differentiation of the macula as Dr Maumenee has described this phenotype. In parallel to the derivation of Latin term, the Greek noun for "place" is "τοπος" ("topos"); the diminutive form would be "τοπιον" ("topion"), the 'small place', thus 'the macula'. Absence of or a failure to develop the macula with purely Greek origin would be "atopion".