Principles and Practice of Clinical Electrophysiology of Vision

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89

Fundus Flavimaculatus–Like Diseases: A Differential Diagnosis; Splitting vs. Lumping

John R. Heckenlively

Patients with yellow lesions scattered in the retina often are a diagnostic problem since there are a number of well-described diseases with yellow dots or flecks (only a few with pathognomonic tests) as well as others that do not fit the pattern of better-described fleck retina diseases (Table 89–1). The picture is further complicated since juvenile macular degenerations with flecks, commonly termed Stargardt's disease, and adult-onset macular atrophy with flecks, or fundus flavimaculatus, are combined under the rubric "Stargardt-fundus flavimaculatus."

There is no standardization on classification of these diseases, and a clear consensus is not currently available, nor is one likely to be forthcoming until distinctive biochemical or gene markers are found. While it is a common viewpoint that Stargardt's disease and fundus flavimaculatus represent the same genetic disorder, there is no scientific evidence that this is true. This would imply that the two disorders arise from mutations at the same gene site.

If basic genetic principles are employed, it is unlikely that an autosomal recessive juvenile-onset case of macular degeneration with flecks is likely to have the same gene defect as an adult-onset one; while conceivably these diseases with different ages of onset could be allelic or have a common pathway defect, it is unlikely that they are the result of the same gene defect. The one known mechanism that could account for a single gene defect with variable expressivity would be secondary gene modifiers, which have not been seen commonly within sibships with fundus flavimaculatus. The typical fundus flavimaculatus phenotype has also been reported in autosomal dominant families[1]; thus at least two genetic forms of fundus flavimaculatus exist.

The historical and diagnostic problem that arises in treating Stargardt's and fundus flavimaculatus as different diseases is that there is often a continuum of findings between those patients who have a juvenile macular degeneration with a few flecks (and possibly a dark choroid) and patients with widely scattered flecks but no macular lesion. It makes no sense to treat the two named disorders as separate diseases when in fact there are overlapping findings. Krill noted a strong similarity between the cases in the original report of Stargardt and patients with typical fundus flavimaculatus, but interestingly he also noted that in his experience there was a second subgroup of patients with fundus flavimaculatus who had severe cone disease on electroretinographic (ERG) and color vision testing.[5] However, the similarity of fundus findings does not make Stargardt's disease and fundus flavimaculatus the same *genetic* disorder. At a clinical level they may be treated as a single disorder (like retinitis pigmentosa [RP] often is), but in the long run, molecular biological techniques are likely to determine that there are a number of different genes and pathogenic mechanisms involved in the clinical entity "Stargardt's–fundus flavimaculatus."

While the above concerns may seem theoretical, they are important because these diseases are studied for gene site or actions. The job of correlating specific gene types to clinical findings will be easier if the starting point is more organized. Because there are a variety of disorders that may mimic fundus flavimaculatus, it is advisable to obtain a baseline

TABLE 89–1.
Differential Diagnosis of Fundus Flavimaculatus

Phenotypic fundus flavimaculatus
Juvenile onset* (Stargardt's disease)
Midadult onset*
Autosomal recessive
Autosomal dominant (uncommon)
Bietti's crystalline retinal dystrophy (see Chapter 90)
Pattern dystrophies (see Chapter 92)
Dominant cone dystrophy (may mimic Stargardt's disease, see Chapter 67)
Inverse retinitis pigmentosa (cone-rod dystrophy) starting with posterior pole flecks or macular atrophy
Retinitis punctata albescens
Oxalosis
Enhanced S-cone sensitivity[7]
Vitamin A deficiency (punctate granular white lesions farther outside the macular area)

*May or may not have a dark choroid effect; it is not known whether the presence of a dark choroid effect is an essential component of the genetic expression.

family history, ERG, Goldmann visual field test, and fundus photographs with fluorescein angiography (with midtransit views of the equator region) on the initial evaluation of these patients.

FUNDUS FLAVIMACULATUS

A historical account of fundus flavimaculatus was described in the previous chapter. While the merging of Stargardt's disease and fundus flavimaculatus into a continuum of disease has been useful in diagnosing a group of diseases and may help in explaining to patients what their prognosis is, there are also limitations to this approach if the patient turns out not to have the clinical course associated with typical fundus flavimaculatus or Stargardt's disease.

Fundus flavimaculatus has been differentiated from other fleck retina diseases by characteristic deep yellow, round or pisciform-shaped lesions deposited within the pigmented epithelium and limited to the posterior pole and posterior equatorial regions. Pigmented lesions are rare. Most but not all cases have the dark choroid effect on fluorescein angiography. If the disease process is at a more advanced stage so that the posterior pole retinal pigment epithelium (RPE) has diffuse hyperfluorescence, the dark choroid effect may be missed on standard macular and disc frames unless views are also taken of the equatorial RPE. If the dark choroid effect is sought in patients with flecks, routine views of retina outside the vascular arcade is recommended.

The dark choroid effect has been shown to be due to an accumulation of intracellular "lipofuscin-like" material in the RPE that blocks the transmission of fluorescein from the choriocapillaris.[2] Of great interest is that the flecks seen clinically are swollen aggregates of debris-filled RPE cells.

CASE STUDIES

It may be useful to briefly look at a number of cases with fundus features that are consistent with what has been called Stargardt's disease or fundus flavimaculatus but whose electrophysiological findings or clinical course has been different from typical cases. An alternative diagnosis is suggested for many of these cases.

Case 1

This 46-year-old woman complained of poor central vision since the age of 40 years. The family history revealed that the parents had common relatives, although the exact relationship between the parents was not known. One brother out of seven siblings also had retinal problems. On presentation her visual acuity was OD 20/50, OS 20/60. Fundus examination revealed severe macular atrophy with only a tiny foveal island left in each eye (Fig 89–1,A), and there were flecks and RPE mottling in equatorial areas. Fluorescein angiography demonstrated a large round defect in the RPE and choroicapillaris that gave an impression of "choroidal sclerosis" (Fig 89–1,B). The ERG showed amplitudes within normal limits on the lower edge of 2 SD with delayed photopic implicit times, and the waveforms could be interpreted as early cone-rod dysfunction. However, this patient likely has fundus flavimaculatus, but because of the advanced nature, the macular area looks similar to the appearance of choroidal sclerosis.

Case 2

This 9-year-old girl presented with visual acuities of OD 20/200, OS 20/400 and a mild myopic correction. She had obvious macular atrophy with inner limiting membrane wrinkling of the posterior pole (Fig 89–2,A). Fluorescein angiography demonstrated a window defect in the macular area with a dark choroid effect outside the macular area (Fig 89–2,B). The visual fields were full, but central scotomas were noted. The ERG was abnormal under

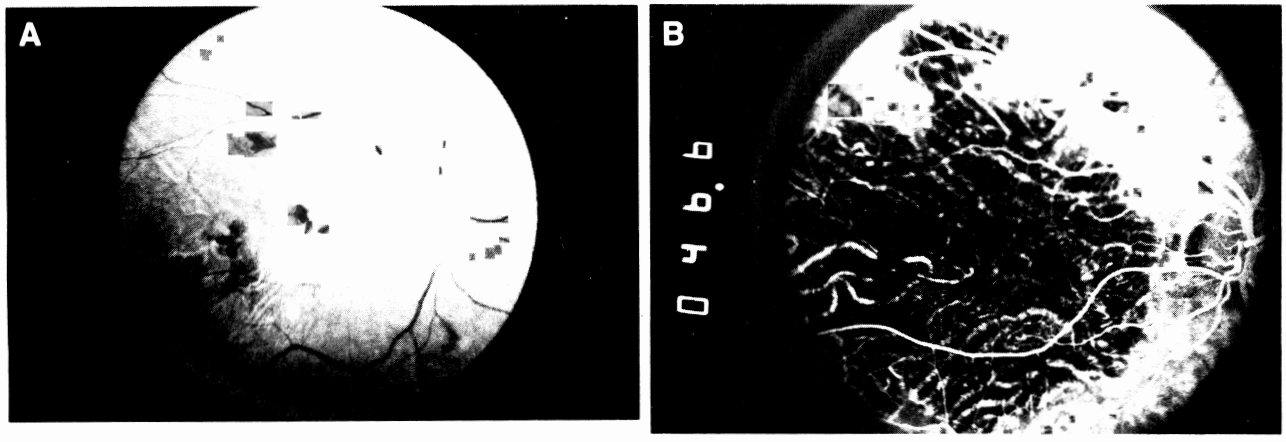

FIG 89–1.
Advanced fundus flavimaculatus. **A,** color photograph showing macular RPE loss and pigmented scarring. **B,** Fluorescein angiogram with the appearance of choroidal sclerosis, but diffuse RPE disease is evident.

photopic and scotopic conditions and had amplitudes approximately 50% of normal. Over the next 10 years, the patient's ERG became nonrecordable, and the central scotoma enlarged and encompassed 30 degrees when measured with the I-4 isopter. This patient who appeared to have a form of Stargardt's disease on presentation (foveal atrophy and dark choroid), is better described clinically as having "retinitis pigmentosa inversa."

Case 3

This 55-year-old woman presented with visual acuities of OD 20/40, OS 20/60 and a history of pho-

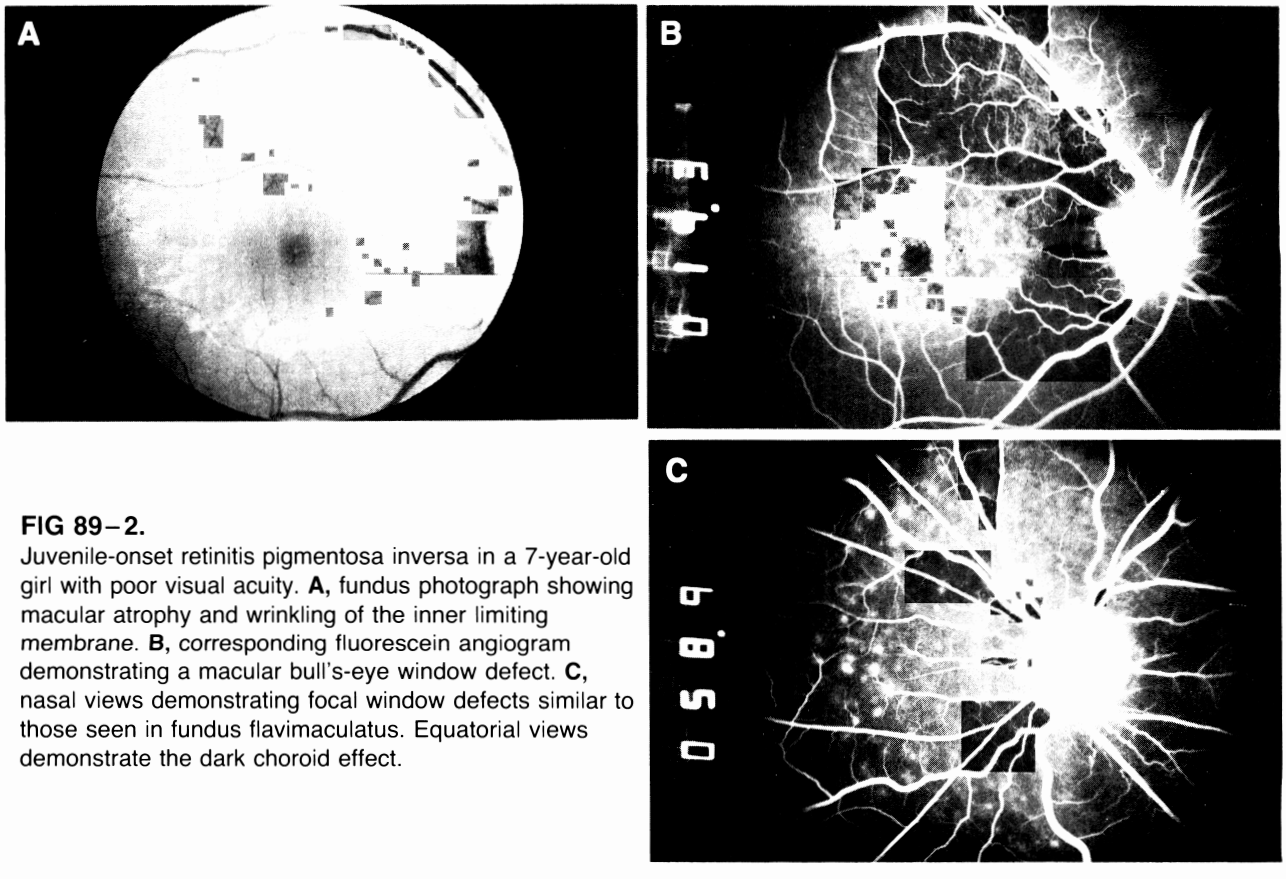

FIG 89–2.
Juvenile-onset retinitis pigmentosa inversa in a 7-year-old girl with poor visual acuity. **A,** fundus photograph showing macular atrophy and wrinkling of the inner limiting membrane. **B,** corresponding fluorescein angiogram demonstrating a macular bull's-eye window defect. **C,** nasal views demonstrating focal window defects similar to those seen in fundus flavimaculatus. Equatorial views demonstrate the dark choroid effect.

topsia, night blindness, and blurred vision OS (Fig 89–3). The family history was negative. ERG testing revealed an abnormal photopic ERG (b-wave amplitudes 45% of a mean age-matched normal), while the rod-mediated ERG was within normal limits. The electro-oculogram (EOG) light-to-dark ratio was OD 130, OS 145. A final rod threshold at 40 minutes showed a 1.15 log unit elevation at 12 and 30 degrees above fixation. Goldmann visual fields demonstrated central scotomas OU. Fundus examination showed numerous yellow flecks widely scattered throughout the posterior pole. The fluorescein angiogram did not have the dark choroid effect.

Over the next 5 years her vision fell to counting fingers in both eyes with a slight enlargement of the central scotomas. This patient appears to have an atypical cone degeneration with posterior pole flecks.

Case 4

This 63-year-old woman presented in May 1973 for evaluation of night blindness of 3 years' duration. There was no known family history or consanguinity. The visual acuity was 20/20 in both eyes. The ERG was barely recordable, and the Goldmann visual fields with the IV-4 target were 10 to 15 degrees in diameter. Funduscopic examination revealed numerous confluent yellow spots of irregular shape that were deep to the retinal vessels and also formed a paramacular ring (Fig 89–4). After 9 years the visual field was reduced to 2 degrees in both eyes with 20/30 visual acuity. The yellow spots disappeared, and obvious panretinal atrophy was present; no sign of the dark choroid effect was found on fluorescein angiography. This case has been reported previously.[3]

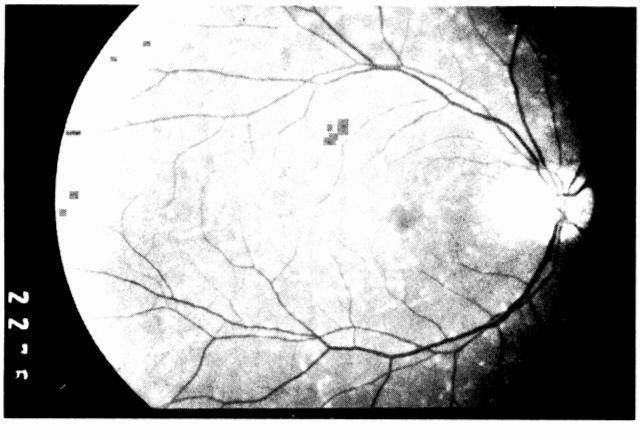

FIG 89–3.
Adult-onset "retinitis pigmentosa" inversa (variety of progressive cone-rod dystrophy) in a 55-year-old woman; a fundus photograph demonstrates extensive posterior pole flecks and foveal atrophy. The ERG was abnormal in a cone-rod pattern, with full peripheral visual fields and expanding central scotomas over time.

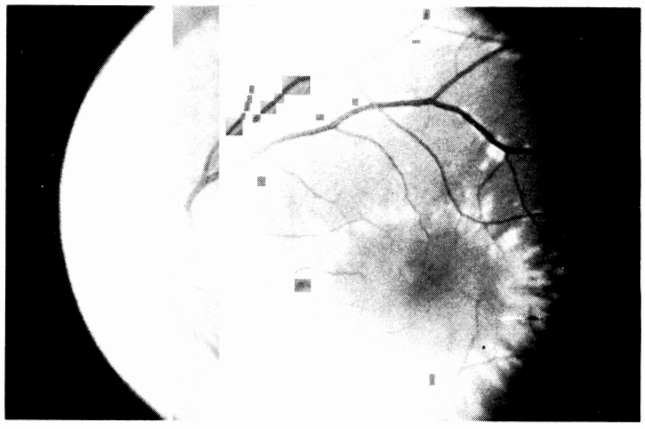

FIG 89–4.
Atypical retinitis punctata albescens in a 63-year-old woman with barely recordable ERGs and yellow deposits in the parafoveal and posterior portions of the retina.

Case 5

This 32-year-old black male presented with a history of glare and some problems reading the eye chart. Both his brother and sister have eye problems. The visual acuity was 20/200 OU. Goldmann visual fields were full with small central scotomas. Fundus examination initially revealed bull's-eye foveal atrophy similar to that seen in Stargardt's disease (Fig 89–5,A), while the fluorescein angiogram demonstrated a diffuse retinal pigment epitheliopathy with a suggestion of the dark choroid effect. ERG testing demonstrated an abnormal photopic b-wave amplitude approximately 40% of mean normal, while the rod-mediated ERG was borderline normal just below 2 SD at 200 μV.

Seven years after his initial visit, he presented with 20/200 vision and a fundus appearance notable for a pseudohypopian-like foveal yellow lesion with scattered yellow deposits throughout the posterior pole (Fig 89–5,B). The fluorescein angiogram with a wide-angle camera demonstrated the dark choroid effect and the RPE disease previously noted (Fig 89–5,C). Repeat ERG testing both in 1987 and 1990 showed abnormal photopic and scotopic ERGs approximately 30% of normal with no evidence of progression between 1986 and 1990 on three ERGs; the Goldmann visual field have remained full. Based on his full visual fields and initial presentation, the patient appears to have an atypical cone degeneration.

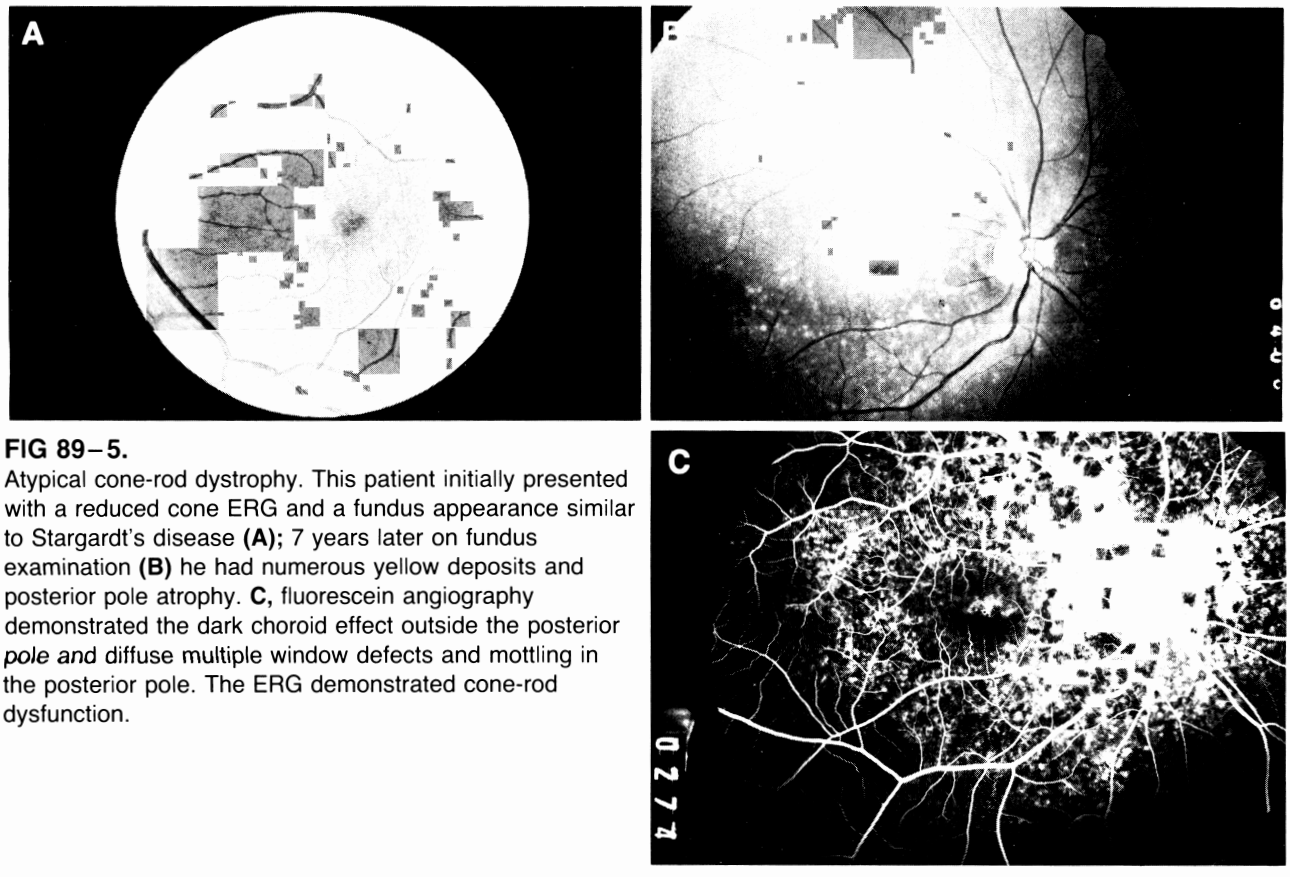

FIG 89–5.
Atypical cone-rod dystrophy. This patient initially presented with a reduced cone ERG and a fundus appearance similar to Stargardt's disease **(A);** 7 years later on fundus examination **(B)** he had numerous yellow deposits and posterior pole atrophy. **C,** fluorescein angiography demonstrated the dark choroid effect outside the posterior *pole and* diffuse multiple window defects and mottling in the posterior pole. The ERG demonstrated cone-rod dysfunction.

Case 6

This 69-year-old woman presented with complaints in reading and nyctalopia so severe that she stopped driving at night. Her best visual acuity was OD 20/60, OS 20/50. Funduscopy demonstrated parafoveal loss and yellow deposits scattered outside the posterior pole similar to some patients with fundus flavimaculatus (Fig 89–6,A). The fluorescein angiogram demonstrated a retinal pigment epitheliopathy without a dark choroid effect (Fig 89–6,B).

ERG testing demonstrated an abnormal photopic

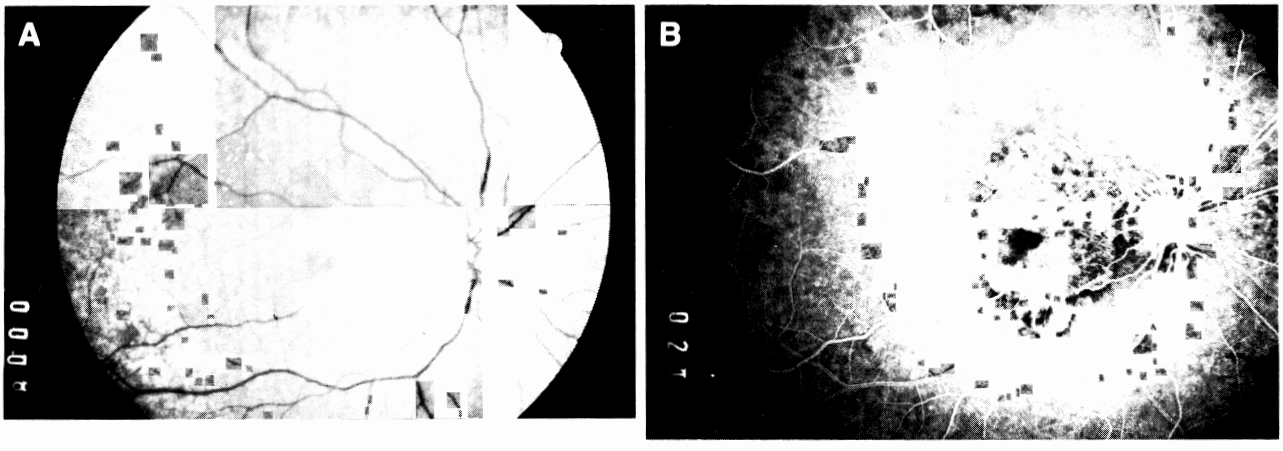

FIG 89–6.
A 69-year-old patient with an abnormal photopic ERG, macular degeneration, and nyctalopia. **A,** a fundus photograph shows parafoveal loss with drusen-like yellow deposits outside the vascular arcades. **B,** a fluorescein angiogram shows a diffuse retinal pigment epitheliopathy with no evidence of a dark choroid and parafoveal loss similar to that seen in fundus flavimaculatus.

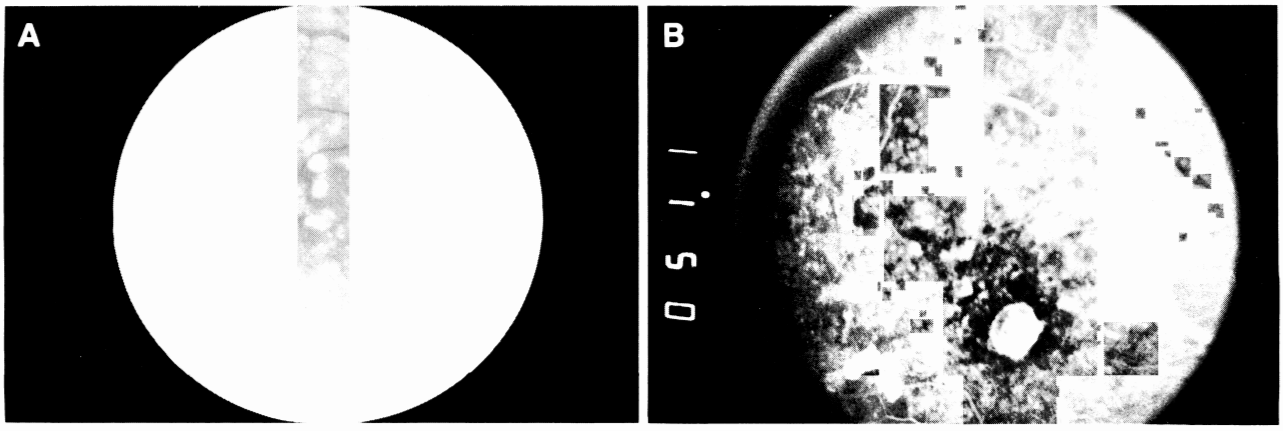

FIG 89–7.
Familial drusen in a 66-year-old man who has a cone degeneration and full visual fields with large central scotomas **(A)** and fleck-like deposits in the posterior pole. **B,** fluorescein angiography showed a diffuse retinal pigment epitheliopathy and foveal window defects with no sign of the dark choroid effect.

ERG 42% of the mean normal for her age group, while the rod-mediated ERG was 78% of mean normal (just below 2 SD). Goldmann visual fields were full but demonstrated small central scotomas. This patient was demonstrating dysfunction of her cone more than her rod system, with a retinal pigment epitheliopathy.

Case 7

This 66-year-old man presented with macular degeneration and visual acuity of OD 20/80, OS 20/60. The patient's brother and father also had similar eye problems. Fundus examination was remarkable for numerous yellow deposits in the macular area (Fig 89–7,A) in both eyes. The fluorescein angiogram demonstrated a diffuse retinal pigment epitheliopathy with areas of focal loss in the macular area (Fig 89–7,B). ERG testing demonstrated an abnormal photopic ERG 40% of the mean normal with a delayed implicit time for his age group and a low normal rod-mediated ERG. Goldmann visual field showed full fields with central scotomas. While the fundus appearance was consistent with familial drusen, the cone ERG was more abnormal than would be expected just from a disease of the macula.

Case 8

This 26-year-old man noted a loss of vision around fixation and was found to have a maculopathy with a reticular pattern of numerous confluent flecks in the macular areas in both eyes (Fig 89–8,A). The fluorescein angiogram showed wide-

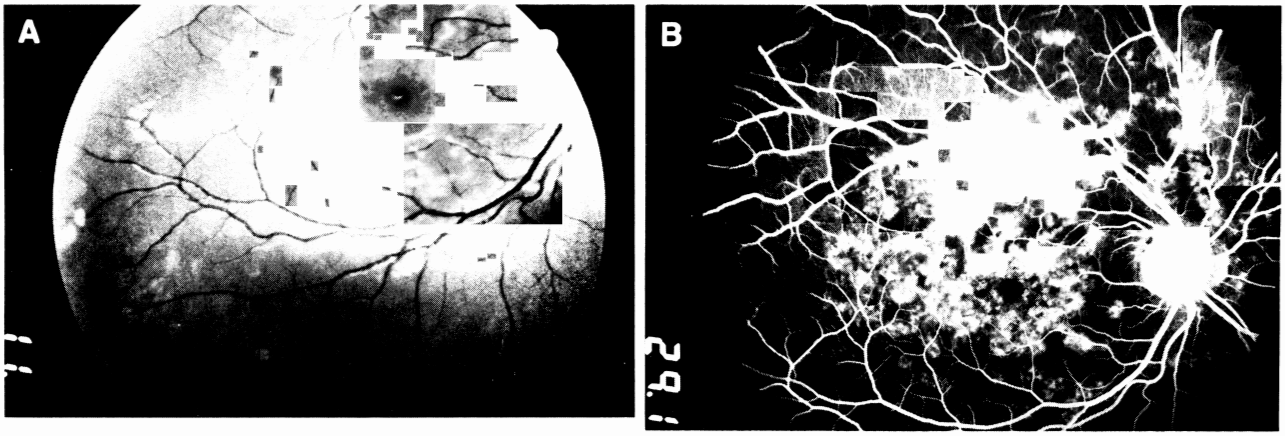

FIG 89–8.
A possible enhanced S-cone syndrome in a 26-year-old man with **(A)** extensive posterior pole flecks and **(B)** a dark choroid effect on fluorescein angiography.

spread focal and confluent window defects and a strong suggestion of the dark choroid effect (Fig 89–8,B). He had no complaints of night blindness, and his visual acuity was OD 20/20, OS 20/200. The photopic ERG was unusual for having a negative wave (a-wave amplitude, 187 μV; b-wave amplitude, 203 μV), while the scotopic and bright-flash dark-adapted ERGs were normal. Goldmann visual fields were full with central scotomas and enlarged blind spots. The fundus appearance is very similar to fundus flavimaculatus, but the ERG is not the same and is similar to findings reported in the "enhanced S-cone syndrome."[7]

One of the first studies reviewing the dark choroid effect in retinal dystrophy was performed by Fish and colleagues who reported 91 cases of posterior pole retinal dystrophy; they examined patients for the presence of a dark choroid, flecks, and bull's-eye lesions and performed electrophysiological testing.[4] A majority of patients had the dark choroid effect either in the periphery or in all of the retina including the posterior pole. Forty-seven patients had flecks at the level of the RPE; of 37 with dark choroids, 34 (92%) had flecks, whereas of 54 patients with normal choroids, only 13 (24%) had flecks. Of 62 patients who had ERG testing, 26 had abnormal photopic ERGs, 8 of whom had dark choroids (Table 89–2).

Macular degeneration is commonly seen in association with retinal flecks, and when the degeneration has a juvenile onset, it has been called Stargardt's disease. In these younger patients, the foveal abnormalities are early and often precede obvious flecks, although the dark choroid effect may be seen on fluorescein angiography. In the adult-onset form, the flecks are usually seen first, and the macular degeneration usually appears years after the initial flecks and is characterized by a parafoveal loss (e.g., Fig 89–8,A) that may leave atrophy of the foveal centralis area (e.g., Fig 89–1,A).

TABLE 89–2.

Summary of the Study by Fish et al. on the Dark Choroid in Posterior Retinal Dystrophies*

Patients studied	91
Dark choroid present	37 (41%)
15/37 (41%) females	
22/54 (41%) males	
White flecks present	47
Dark choroid present	34 (92%)
Dark choroid, no flecks	3 (8%)
(All had bull's eye macular disease)	
Normal choroid present	54
Flecks present	13 (24%)
Electro-oculogram (59 patients)	
Abnormal (<180 L/D)	40/59 (68%)
Dark choroid	16/22 (73%)
Electroretinogram results	(62 patients)
Abnormal photopic ERG	26/62 (42%)
Dark choroid	8/23 (35%)
Normal choroid	18/39 (46%)
Abnormal scotopic ERG	10/62
Dark choroid	2/23 (9%)
Normal choroid	8/39 (21%)

*Data from Fish G, Grey R, Sehmi KS, Bird AC: *Br J Ophthalmol* 1981; 65:359–363.

ELECTROPHYSIOLOGICAL FINDINGS

ERG testing of fundus flavimaculatus and Stargardt's disease usually gives waveforms that are within normal limits for the patients' age, although the amplitudes are frequently low normal. A few cases of advanced fundus flavimaculatus with extensive posterior pole atrophy may have abnormal ERGs, often in a cone-rod dysfunction pattern; the dark choroid effect on the fluorescein angiogram may be the definitive finding to help make the diagnosis in these patients if there are not fundus photographs from previous years that document typical fundus flavimaculatus flecks. The EOG is typically abnormal in most of the fleck retina diseases and has not been demonstrated to be useful in distinguishing types of fleck retina. The c-wave on DC-ERG tends to follow the values found on the EOG.[8]

Lachapelle et al. compared the ERGs of six patients with typical fundus flavimaculatus and no macular involvement with nine patients who had Stargardt's disease and macular atrophy without fish-tail flecks, although some patients had peripheral flecks or RPE mottling. This study found that the patients with fundus flavimaculatus had photopic and scotopic amplitudes 58% and 64% of normal, respectively, while patients with Stargardt's disease had amplitudes 33% and 34% of normal.[6]

If a patient thought to have fundus flavimaculatus demonstrates highly abnormal electrophysiological findings, then other disease processes should be considered. Because fundus flavimaculatus can mimic other diseases, it is recommended that *at least one baseline ERG be done* in these patients to assess the physiological status of the eye and to ensure that an RP-like process or cone degeneration is not present. A follow-up ERG in 5 to 10 years may clarify whether the disease process in question is progressive. This issue is important clinically because patients want to know whether they are getting worse.

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