Principles and Practice of Clinical Electrophysiology of Vision

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Stargardt's Disease—Fundus Flavimaculatus

Kenneth G. Noble

HISTORY

In a series of publications beginning in 1909, Stargardt[17] described the essential features of this disease that would bear his name. Fifty-four years later Franceschetti[9] coined the term *fundus flavimaculatus* (FF) to describe an unusual fundus appearance occurring in the posterior pole of middle-aged individuals with or without macula degeneration.

The typical fundus appearance of Stargardt's disease, which was indeed described and depicted in his publications, is a pigmentary maculopathy surrounded by yellowish white spots or "flecks." In the typical case of FF it is the flecks that are most impressive because they occupy the posterior pole and extend out to the midperiphery, and macula abnormalities may or may not be evident.

The similarity of the fundus picture in these two disorders was noted by a number of authors,[11, 13] and studies of large groups[1, 10, 15] have suggested that they are different phenotypic manifestations for the same genetic disease. For the purposes of this discussion the diseases will be considered as one and referred to as Stargardt's FF.

INTRODUCTION

Stargardt's FF is classified as a hereditary macular dystrophy. It is the most common macular dystrophy and serves, in much the same way as does retinitis pigmentosa for the generalized retinal dystrophies, as the prototype for these disorders.

In the most typical and common presentation, a child in the first two decades of life complains of central visual difficulty associated with a bilateral symmetrical pigmentary maculopathy (with or without flecks). Test results of general retinal function (e.g., the electroretinogram) are normal, and the course is slow visual deterioration over a period of years to levels of 20/100 to 20/400. There appears to be no gender, racial, or ethnic predilection.

INHERITANCE

An autosomal recessive mode of inheritance has been firmly established.[1, 10, 15] Therefore, when taking a history one should inquire about affected siblings and parental consanguinity.

Dominantly inherited macular dystrophies have been reported and reviewed by Deutman,[4] who concluded that they were most likely progressive cone dystrophies. There is a well-documented pedigree of a dominant macular dystrophy in which there was a variable phenotypic expression with some family members showing a typical appearance of Stargardt's FF while other members had minimal foveal depigmentation or marked macular choroidal atrophy.[3] In another family in which four affected members from three successive generations were examined, the youngest individual, aged 17 years, showed the typical fundus picture, the eldest (aged 82 years) showed massive chorioretinal atrophy with an extinguished electroretinogram, and the two members of middle age showed macular atrophy without flecks and a normal electroretinogram.[18]

AGE AT ONSET

In the great majority of individuals the onset of visual symptoms occurs between the first and third decades of life, and this prompted the alternative

name juvenile macular degeneration. However, large studies report that a significant number of individuals may be asymptomatic into the fourth through sixth decade and even into the eighth decade.[1, 10, 15]

When the age at initial presentation is in the later decades, the diagnosis may not be suspected, even when the fundus appearance is typical. If the fundus appearance is atypical, the diagnosis will certainly not be suggested. Helpful clues in making the diagnosis in these circumstances is the bilaterality and symmetry of the maculopathy as well as the typical fluorescein angiographic appearance (see the later section on fluorescein angiography).

VISUAL ACUITY

Since the macula is invariably affected in this disorder, the initial complaint is related to central visual loss. The presenting visual acuity may range from 20/20 to 20/200, with most patients having vision somewhere between these values. At the time of presentation the visual acuity loss may occasionally be markedly asymmetrical. Unfortunately the better-seeing eye will catch up as both eyes undergo a steady progression. While final vision worse than 20/400 is uncommon, it has been noted. Long-term follow-up on these patients into the sixth decade and longer may indicate that continued visual loss worse than 20/400 is not that infrequent.

FUNDUS APPEARANCE

At the time of presentation the fundus morphology will be bilateral and symmetrical. The most typical appearance (seen in some of Stargardt's patients) is a pigment abnormality in the macula that is

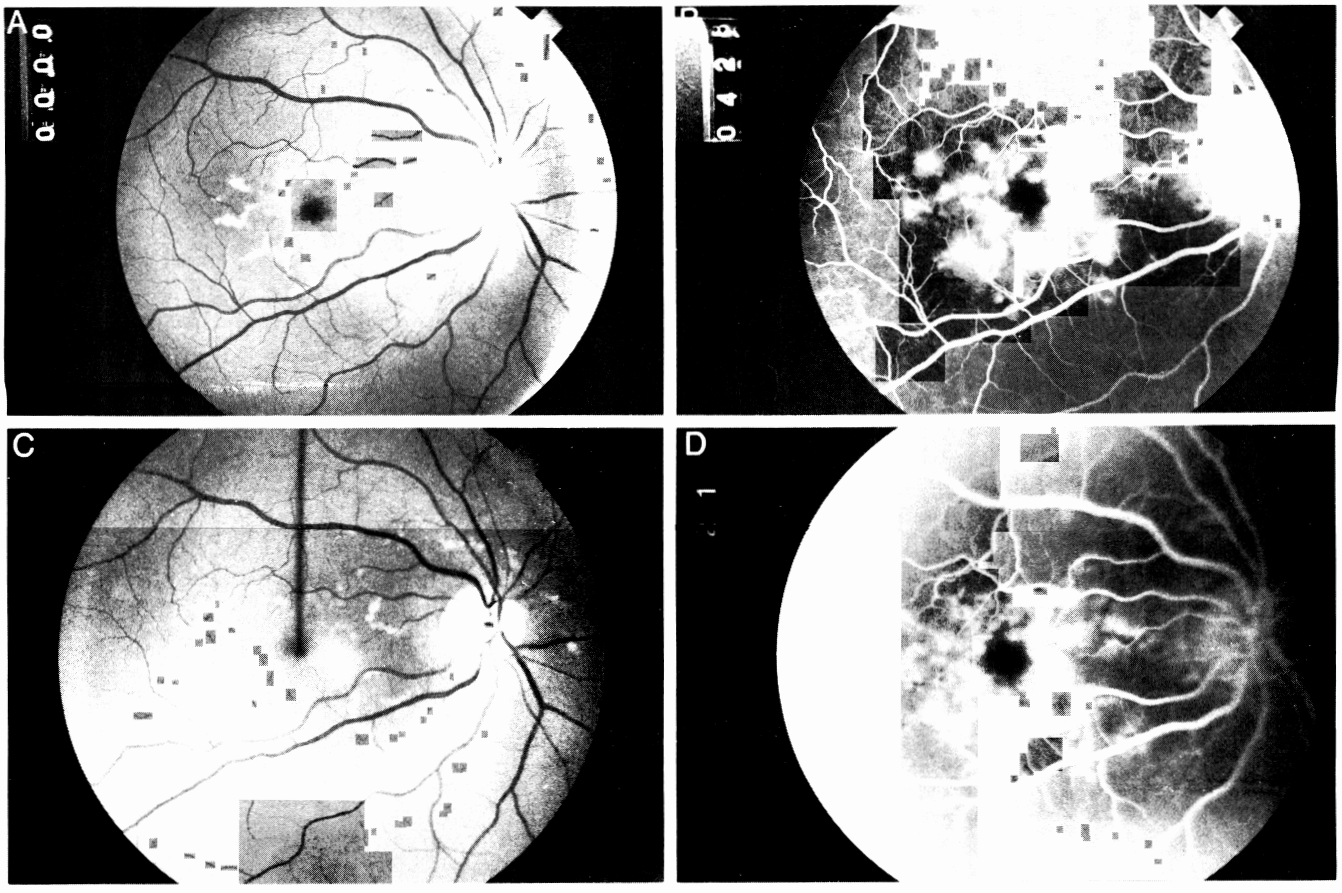

FIG 88–1.
Fundus flavimaculatus. **A,** at initial presentation the fundus shows a mild foveal granularity surrounded by irregularly shaped yellowish white flecks **(B).** The fluorescein angiogram shows focal areas of transmitted hyperfluorescence that do not correspond directly with the flecks as well as a normal background choroidal fluorescence **(C).** 3 years later, comparison shows a change in the shape of many of the previous flecks **(D).** Similarly, the fluorescein angiogram shows a change in appearance.

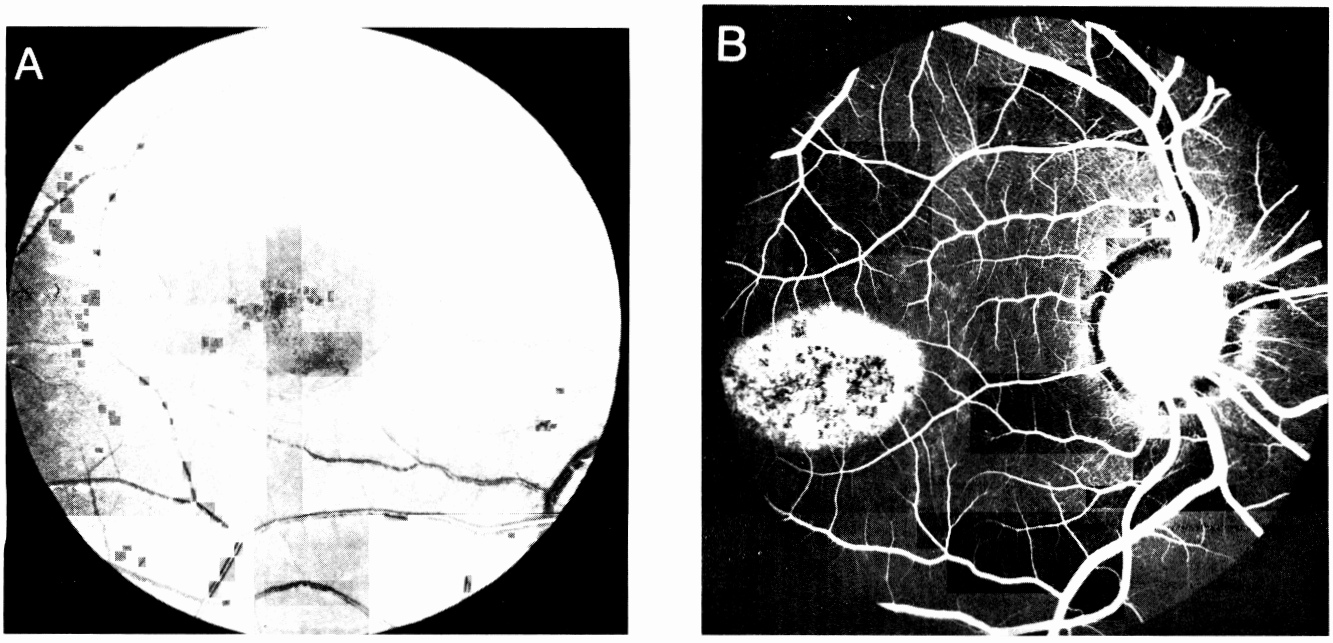

FIG 88–2.
Stargardt's fundus flavimaculatus. **A,** the macula has a mild pigment granularity associated with an irregular light reflex. No flecks are seen **(B).** The fluorescein highlights the pigment disturbance in the macula. The underlying choroidal fluorescence is not evident, and the details of the retinal capillaries are contrasted against a darkened background (dark choroid effect).

surrounded by a few irregularly shaped yellowish white flecks deep in the retina. (Fig 88–1) However, the appearance may be quite varied.

In some individuals the only abnormality is a mild pigment abnormality in the macula that is unassociated with any flecks (Fig 88–2). Many will subsequently develop flecks. Others present with diffuse flecks and either a normal-appearing macula or an obvious macular disturbance (Fig 88–3, Plate 16).

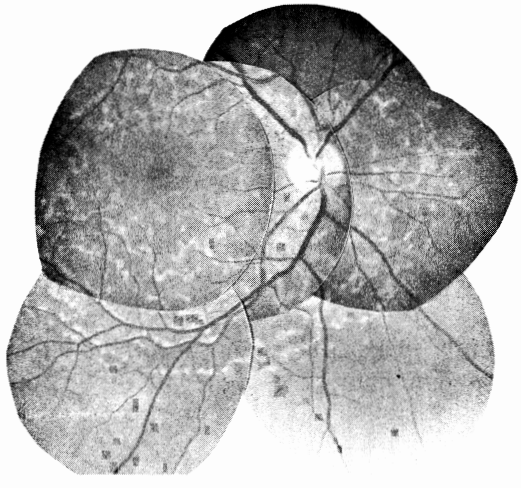

FIG 88–3.
Fundus flavimaculatus. There are diffuse flecks in the posterior pole and beyond the vascular arcades. The vision was 20/20, and the macula appeared unaffected. **(See also Color Plate 16.)**

Other appearances include a marked tapetal reflex ("beaten bronze") (Fig 88–4), choroidal atrophy, bull's-eye maculopathy, bone spicule pigment clumping, and subretinal choroidal neovascularization. While these unusual appearances may suggest alternative diagnoses, an unusual fundus morphology, by itself, should not dissuade one from entertaining the diagnosis of Stargardt's FF.

When these patients are observed over a number of years, the changing fundus pattern is apparent. In general, the pigment abnormalities in the macula become more profound, although not always associated with concomitant visual loss. The flecks are continually disappearing and reappearing elsewhere. Sometimes they leave no trace; at other times, a mild pigmentary abnormality is noted. On occasion, focal areas of chorioretinal atrophy are the sequelae of absorbed flecks (see Fig 88–1).

FLUORESCEIN ANGIOGRAPHY

Fluorescein angiography has proved to be helpful in a number of ways in this disease. When a subtle maculopathy is suspected, the mild pigmentary alterations will be confirmed by a transmitted hyperfluorescence. When a maculopathy is obvious but

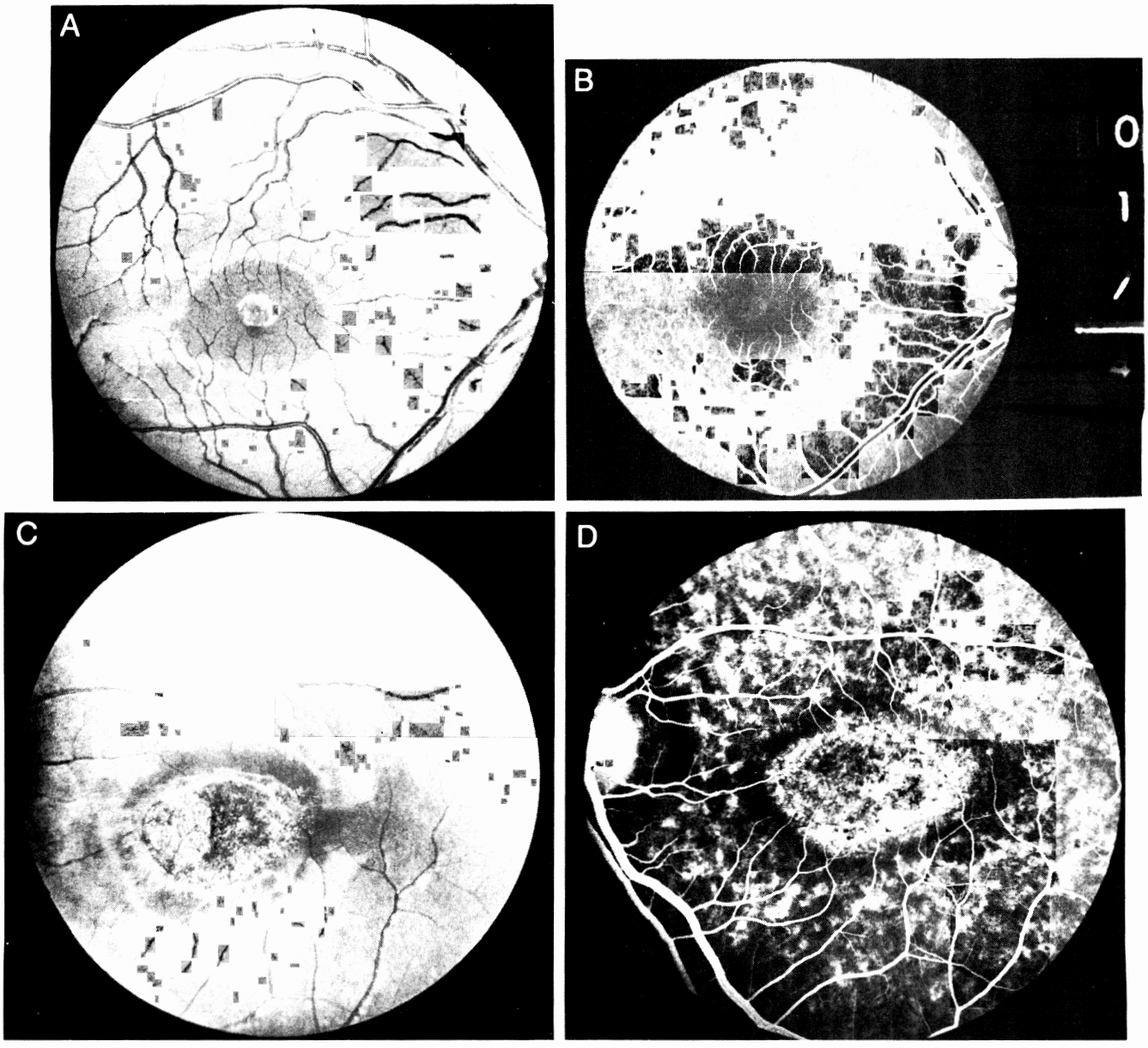

FIG 88–4.
A maculopathy was suspected because of a diffuse "beaten-bronze" reflex in the macula, and this was confirmed by a mild degree of transmitted hyperfluorescence (**A** and **B**). In this patient the maculopathy was obvious, but there were no flecks present. The fluorescein angiogram demonstrated more widespread involvement of the posterior pole (**C** and **D**).

flecks are not visible, the angiogram may show patchy areas of hyperfluorescence in the posterior pole that indicate a more diffuse involvement (see Fig 88–4).

Finally, in a large majority of patients (86% in one study)[8] there is an absence or decrease in the normal background choroidal fluorescence (referred to as the "silent" or "dark" choroid)[2, 6] (see Fig 88–2). This warrants special attention because it occurs so frequently, it is rarely found in other retinal disorders, and it may be related to recent pathological studies (see the later section on pathology).

VISUAL FUNCTION STUDIES

Extensive psychophysical and electrophysiological testing has been performed on many individuals at

various "stages" in the disease. Unfortunately, while these tests are helpful, they are not diagnostic.

The single most important test is the electroretinogram because this will distinguish between a generalized retinal dystrophy (e.g., retinitis pigmentosa) and a localized retinal dystrophy. Early in the course of the disease the electroretinogram is usually normal. The most common abnormality that may occur is a decrease in the photopic b-wave amplitude, usually with a normal implicit time.[1, 15] In the more advanced disease both the photopic and scotopic responses may be abnormal.[7]

The electro-oculogram in most cases is normal, but there are some individuals who will show an abnormal electro-oculogram with a normal electroretinogram.[10, 15] Other than this electrophysiological dichotomy there is no other distinguishing feature of these individuals.

A recent study[16] evaluated macular function by utilizing the focal electroretinogram in normal subjects, in patients with retinitis pigmentosa and good vision (20/20 to 20/60), and in patients with Stargardt's FF (vision range from 20/30 to 20/200). The patients with retinitis pigmentosa showed a selective loss of the focal electroretinographic responses at the higher temporal frequencies (30 to 60 Hz), whereas the patients with Stargardt's FF showed an amplitude loss at both the high and low temporal frequencies. The loss at the high temporal frequencies may represent changes in the membrane time constant. While the frequency loss in both these diseases is receptoral in origin, the pathogenetic mechanism of receptor damage in either disease is not apparent.

PATHOLOGY

The initial histopathological study[12] of a patient with FF showed that the major abnormality resided in the retinal pigment epithelium (RPE), which had an altered morphology and an abnormal accumulation of intracellular materials. A subsequent report[5] expanded on these findings by means of ultrastructural, autofluorescent, and histochemical studies. There was a "massive intracellular accumulation of an abnormal lipofuscin-like substance" within the RPE that was present throughout the retina but most marked in the posterior pole. It has been suggested that the abnormal lipofuscin accumulation may be responsible for the "dark" choroid seen on angiography since this pigment will absorb the underlying choroidal-transmitted fluorescence.

One additional report[14] did not find these abnormalities in the RPE but found distended apices of the RPE that were filled with "lipid membranes with a tubulovesicular appearance." These conflicting findings suggest either different "stages" of the disease or perhaps two distinct pathogenetic mechanisms leading to a similar clinical picture.

PATHOGENESIS

The pathogenesis of this disorder is not known. Based on the fundus appearance, visual function tests, and histopathology the most likely primary site of disease would be the RPE-photoreceptor complex. The macula is the most vulnerable and frequent location. However, in a number of cases the RPE-photoreceptor abnormality may extend into the midperiphery.

TREATMENT

There is no known treatment.

PROGNOSIS

Since this disease has been classified as one of the hereditary macular dystrophies, it had been felt that while the central retinal elements would continue to degenerate, the disease would not spread centrifugally, i.e., would not evolve into a generalized retinal dystrophy. There now seems to be two pieces of information that belie this assumption.

Fishman[7] classified FF from a mild stage 1 having localized central disease with normal test results of general visual function to an advanced stage 4 with extensive chorioretinal atrophy and abnormal test findings of general visual function. While this study did not follow the progression of patients over a period of time, the implicit understanding was that in some individuals there may be a steady progression from one stage to another.

Aaberg[1] did follow patients over a period of time to assess whether in fact there was such progression. Approximately one quarter of the 56 patients did advance at least one stage, and 5 patients advanced from a mild stage to an advanced stage. These 5 patients had the longest follow-up.

The long-term prognosis may not be as benign as previously thought. It may well be that as these youngsters with juvenile macular dystrophy reach the sixth decade and beyond, some may develop the

picture and findings of a generalized retinal dystrophy.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of this disorder is based on the fundus appearance at the time of presentation. When the primary finding is in the macula, an unusual appearance may suggest diseases such as central areolar choroidal dystrophy, vitelliform macular dystrophy, progressive cone dystrophy, chloroquine toxicity, and the later atrophic stage in X-linked retinoschisis. The mode of inheritance and visual function tests (and chloroquine levels if toxicity is suspected) should distinguish among these diseases.

When the predominant fundus picture is the yellowish white flecks, the differential diagnoses include drusen of Bruch's membrane, fundus albipunctatus, retinitis punctata albescens, multiple vitelliform cysts, the flecked retina syndrome of Kandori, and certain pattern dystrophies of the RPE. Once again, the mode of inheritance and visual function tests are helpful in eliminating a number of these disorders. Furthermore, the irregular linear, pisciform shape of FF once appreciated, is not usually confused with these other disorders.

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REFERENCES

1. Aaberg TM: Stargardt's disease and fundus flavimaculatus: Evaluation of morphologic progression and intrafamilial coexistence. *Trans Am Ophthalmol Soc* 1986; 84:453–487.
2. Bonin P, Passot M, Triolaire MTH: Le signe du silence choroidien dans les degenerescences tapetoretiennes posterieures. *Doc Ophthalmol* 1976; 9:461–463.
3. Cibis GN, Morey M, Harris DJ: Dominantly inherited macular dystrophy with flecks (Stargardt). *Arch Ophthalmol* 1980; 98:1785–1789.
4. Deutman AF: Macular dystrophies, in Goldberg MF (ed): *Genetic and Metabolic Eye Diseases*. Boston, Little Brown & Co, Inc, 1974, p 385.
5. Eagle RC Jr, Lucier AC, Bernardino VB Jr, Yanoff M: Retinal pigment epithelial abnormalities in fundus flavimaculatus. A light and electron microscopic study. *Ophthamology* 1980; 87:1189–1200.
6. Fish G, Grey R, Sehmi KS, Bird AC: The dark choroid in posterior retinal dystrophies. *Br J Ophthalmol* 1981; 65:359–363.
7. Fishman GA: Fundus flavimaculatus. A clinical classification. *Arch Ophthalmol* 1976; 94:2061–2067.
8. Fishman GA, Farber F, Patel BS, Derlacki, DJ: Visual acuity in patients with Stargardt's macular dystrophy. *Ophthalmology* 1987; 94:809–814.
9. Franceschetti A: Ueber tapeto-retinal degeneration im kindesalter, in Sautter H (ed): *Entwicklung und Fortschritt in der Augenheilkunde*. Stuttgart, West Germany, F Enke, 1963, pp 107–120.
10. Hadden OB, Gass JDM: Fundus flavimaculatus and Stargardt's disease. *Am J Ophthalmol* 1976; 82:527–539.
11. Irvine R, Wegeland FL Jr: Stargardt's hereditary progressive macular degeneration. *Br J Ophthalmol* 1976; 82:527–539.
12. Klein BA, Krill AE: Fundus flavimaculatus; clinical, functional and histopathologic observations. *Am J Ophthalmol* 1967; 64:3–23.
13. Krill AE, Deutman A: The various categories of juvenile macula degeneration. *Trans Am Ophthalmol Soc* 1972; 56:817–825.
14. McDonell PJ, Kivlin JD, Maumenee IH, Green WR: Fundus flavimaculatus without maculopathy. A clinicopathologic study. *Ophthalmology* 1986; 93:116–119.
15. Noble KG, Carr RE: Stargardt's disease and fundus flavimaculatus. *Arch Ophthalmol* 1979; 97:1281–1285.
16. Seiple WH, Siegel IM, Carr RE, Mayron C: Evaluating macular function using the focal ERG. *Invest Ophthalmol* 1986; 27:1123–1130.
17. Stargardt K: Ueber familiare, progressive degeneration in der makulagegend des auges. *Graefes Arch Ophthalmol* 1909; 71:534–550.
18. Wu G, Weiter JJ, Hirose T: Autosomal dominant Stargardt's disease. *Ophthalmology* 1987; 94(suppl):116.