Principles and Practice of Clinical Electrophysiology of Vision

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Congenital Stationary Night Blindness

Ronald E. Carr

Congenital stationary night blindness (CSNB) has been a well-recognized entity since 1838 when Cunier[8] described a seven-generation family in southern France with poor night vision but perfectly normal visual functions in all other respects. This genealogy was expanded, other geologies were described throughout the world, and in time a number of separate entities were described, all of which had in common a stationary abnormality of dark adaptation.

This group of disorders can now be classified as follows:

I. CSNB with normal fundi (autosomal recessive, autosomal dominant, X-linked recessive)
   A. Absent scotopic electroretinogram (ERG) (Riggs type; type I)
   B. Negative ERG (Schubert-Bornschein; type II)
      1. Complete
      2. Incomplete

II. CSNB with abnormal fundi
   A. Oguchi's disease
   B. Fundus albipunctatus
   C. Fleck retina of Kandori

CONGENITAL STATIONARY NIGHT BLINDNESS WITH NORMAL FUNDI

One of the largest and most complete genealogical records in ophthalmology is that of the Nougaret family of France. By 1907 the genealogy encompassed nine generations; included 2,121 persons, of whom 135 were night-blind; and firmly established an autosomal dominant mode of heredity.[26]

An X-linked mode of heredity of CSNB was documented in the mid-1800s,[9] and later it was recognized that CSNB was also inherited as an autosomal recessive trait.[12] While early psychophysical studies seemed to show that there were two forms of CSNB, one with normal cone function and one with somewhat impaired cone function, it has been only recently, with the advent of more sophisticated electrophysiological studies, that a much clearer understanding of the various forms of CSNB became apparent.[1, 2] Classification of these stationary night-blinding disorders has been primarily by ERG changes, if possible correlated with inheritance pattern.

There are two types of ERGs in these disorders (Fig 96–1), one in which there is a reduced-amplitude photopic response that does not increase in darkness (type I, Nougaret type) and the second in which the most striking abnormality is an absence of the dark-adapted, bright-flash ERG b-wave (type II, Shubert-Bornschein type). Indeed, the absence of b-wave responsiveness brings out the a-wave to a greater extent than normally seen. In this type the photopic response is likewise reduced.

In a series of studies Carr et al.[6, 7] were able to demonstrate that the type I ERG showed normal visual pigment kinetics, with the abnormalities of the ERG pointing to an abnormality in transmission in the inner segments of the photoreceptors. Type II, again with normal visual pigments and a normal ERG a-wave, would seem to have an abnormality in neural transmission in the bipolar cell region. A series of electrophysiological and psychophysical studies suggested that within this inner nuclear layer the interplexiform cell may be the primary cell implicated in this disease.[30] Histological studies on both forms of CSNB[33, 34] showed no structural abnormal-

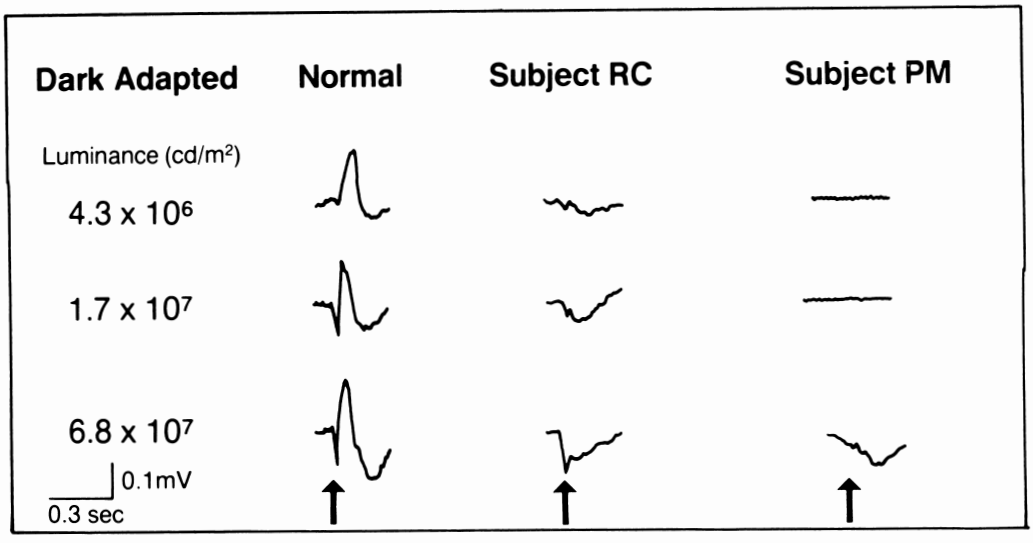

FIG 96–1.
CSNB, normal fundi. The dark-adapted ERGs are shown for a normal individual, a patient with a deep negative dark-adapted response *(RC)*, and a patient with a very small dark-adapted response no different in character than the light-adapted ERG *(PM)*.

ities, and a report on the nyctalopic Appaloosa horse with type II CSNB likewise showed normal histology.[35] This absence of any overt abnormality gives further credence to these hypotheses regarding the site of the abnormality.

The ERG findings of type I tie in well with the psychophysical changes, with the absence of a rod-cone break on dark adaptation indicating no rod function (Fig 96–2). The ERG findings of type II are more complex, with two types of ERG findings

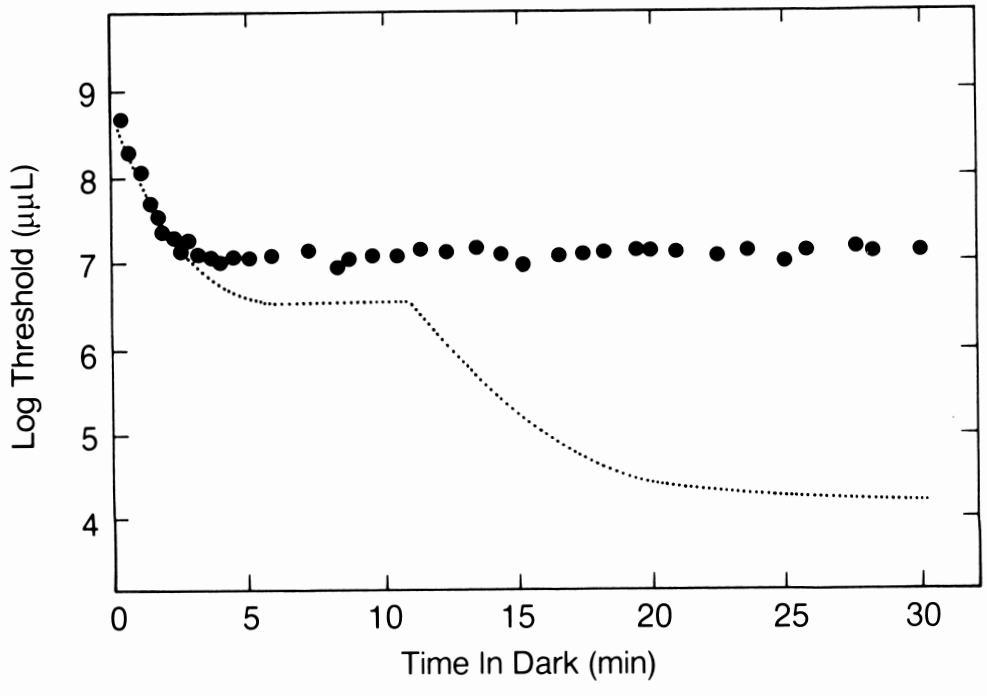

FIG 96–2.
CSNB, Normal fundi. This dark adaptation curve of a normal individual *(dotted line)* shows a normal bipartite curve. The patient with CSNB *(filled circles)* shows no rod dark adaptation: cone threshold is slightly elevated.

noted. Miyake and coworkers[21] have used the terms *complete* and *incomplete* to describe these two varieties, and these variants will be more fully described in Chapter 97.

It has long been recognized that there is an X-linked recessive form of CSNB that in some cases is associated with moderate or severe myopia, decreased vision, and nystagmus. While several reports of female carriers showed no predictable changes, Miyake and Kawase[22] showed a loss of electro-oculogram (EOG) oscillations in the female carrier of this hereditary variety. This is not the only report of abnormalities in the oscillatory potentials, for patients with other forms of CSNB may show such changes.[14]

CONGENITAL STATIONARY NIGHT BLINDNESS WITH ABNORMAL FUNDI

Oguchi's Disease

In 1907 Oguchi[28] described an unusual form of CSNB that was characterized by a peculiar gray-white discoloration of the retina. This gave a metallic sheen to the back of the eye. The vessels stood out in marked relief against the background, and the maculae appeared abnormally dark in contrast to their surround. He presented this entity in greater detail in 1912[27] when he described three cases. He noted that the discoloration did not have to be throughout the retina but instead might be confined to either the posterior pole or equatorial regions. In 1913 Mizuo[23] described a peculiar fundus finding in this disorder, a change now known as Mizuo's phenomenon. In cases of Oguchi's disease, after prolonged adaptation, he noted that the unusual fundus coloration disappeared and the retina appeared perfectly normal (Fig 96–3). After exposure to light the retina then slowly reverted back to its original metallic color.

The autosomal recessive mode of inheritance of this disorder was evident even in Oguchi's original cases[27] where consanguinity was known in two of the three pedigrees. This was confirmed in the large study of Takagi and Kawakami,[32] who presented three of their own cases, reviewed the 56 cases described up to that time, and found the incidence of consanguinity to be 62%.

While the abnormal fundus coloration served to distinguish this variety of CSNB from CSNB with normal fundi, the psychophysical course of dark adaptation was likewise found to be very different. Nakamura[25] demonstrated that following prolonged adaptation most of the patients showed a slow fall in thresholds until normal levels were reached (Fig 96–4). The time was variable, ranging from 2 to 24 hours. Nakamura then subdivided the cases of Oguchi's disease based on their dark adaptation properties and the presence or absence of Mizuo's phenomenon. Type I, the most common, showed both

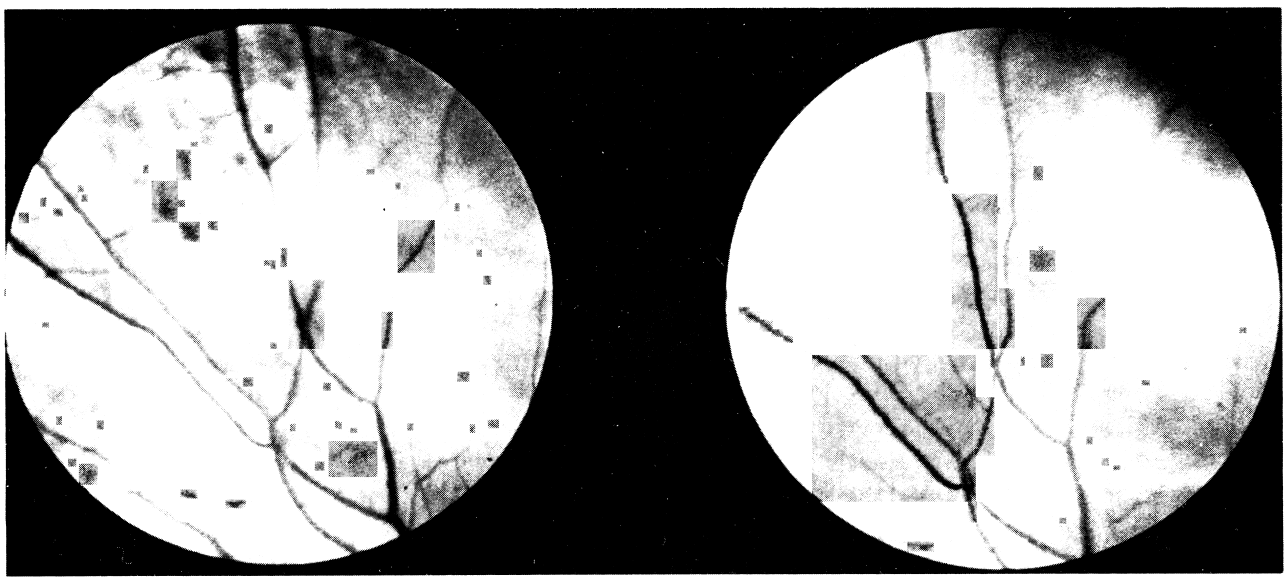

FIG 96–3.
Oguchi's disease. *Left*, light-adapted retina showing a metallic-like reflex; *right*, after 4 hours' dark adaptation the retina appears normal.

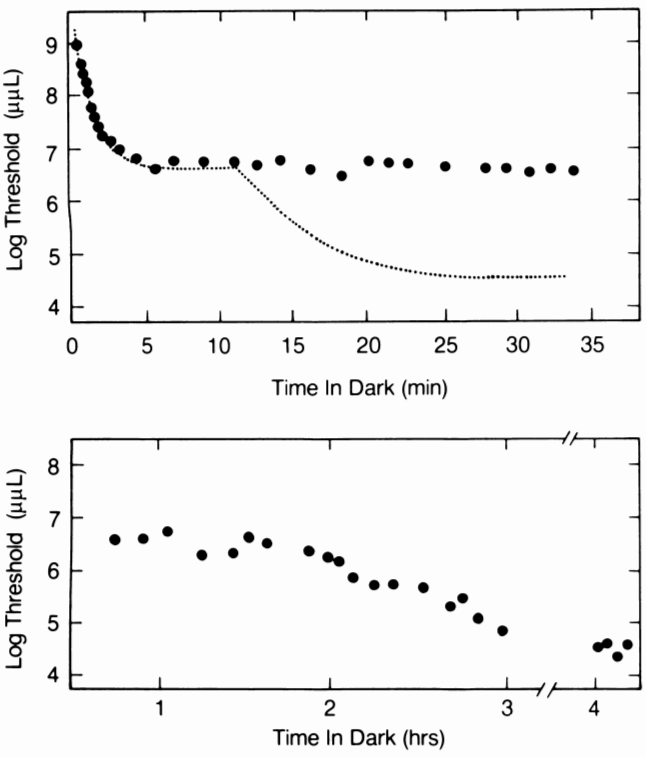

FIG 96–4.
Oguchi's disease: dark adaptation curve. *Top*, normal person represented by a *dotted line.* The patient with Oguchi's disease *(filled circles)* does not come down to a normal rod level at 30 minutes. *Bottom*, a normal rod threshold is reached after 4 hours of dark adaptation.

Mizuo's phenomenon and a slow fall in adaptation, type IIA showed Mizuo's phenomenon but no change in adaptation from the cone threshold, and type IIB did not show Mizuo's phenomenon nor a change in adaption. These latter types thus showed dark adaptation curves similar to what is seen in CSNB without fundus changes. It was during the course of these early studies that it was recognized that Mizuo's phenomenon was not related to threshold change, a finding that was subsequently confirmed in later, more detailed studies.[3, 4]

The first electrodiagnostic investigations of Oguchi's disease were carried out by Hirose,[15] who demonstrated an absent b-wave, and later by Nagata,[24] who found some evidence of scotopic function. In 1965 Carr and Gouras[3] presented a detailed ERG analysis of the disease. To further elucidate the ERG pattern following prolonged adaptation, computer summation techniques were used. By the use of a low-intensity red light selected so as not to adapt the patient, they found a normal cone response but an abortive rod response that was both reduced in amplitude and markedly increased in latency. This discrepancy between threshold and ERG responses was eventually resolved by Gouras,[13] who found a normal scotopic ERG response to the initial ERG stimulus but a loss of this scotopic response to subsequent stimuli. Thus the light required to elicit a b-wave is sufficient to desensitize the retina.

Because of these unusual adaptation characteristics as well as the fundus color changes during dark adaptation, many authors postulated that this disorder was due to an abnormality in rhodopsin kinetics, one in which there was possibly a greatly retarded resynthesis of this visual pigment. However, the study of Carr and Ripps[4] that measured in vivo the concentration and kinetics of the visual pigments in a patient with Oguchi's disease proved this not to be the case. In a full series of psychophysical and electrophysiological studies they showed that rhodopsin was normal in both amount and regenerative properties and also that rhodopsin photosensitivity was normal (Fig 96–5,A and B). It may be that this disease is related to an abnormality of network adaptation, but such a hypothesis lacks any concrete support.

Attempts to define the pathological abnormality in Oguchi's disease date back to Yamanaka[36] and Oguchi[29] in the mid-1920s. The former had the first opportunity to do histological studies on such a case but, in addition, presented one half of the eye he had acquired to Oguchi for parallel investigation. There were, however, important differences in their reports, and the very marked differences in interpretation make these reports of historical interest only. It was not until 40 years later, in 1963, that Kuwabara and associates[19] had the opportunity to study another eye with this disease. In this excellent histopathological and electron microscopic study several findings were noted. The authors noted the existence of an abnormal layer between the outer segments of the photoreceptors and the pigment epithelial cells. However, the constituents of this layer were not pathological but were normal components of the retina consisting of fuscin granules and protrusions of the pigment epithelium with complex interdigitations of the outer segments. The pigment epithelial cells themselves were normal with an abnormal complement of fuscin granules. The outer segments of both rod and cone receptors had abnormal cytoplasm showing microvacuolar or tubular internal structures instead of ordinary lamellae. These abnormalities in the photoreceptors may help in understanding the electrophysiological abnormalities, but a definitive explanation encompassing the psy-

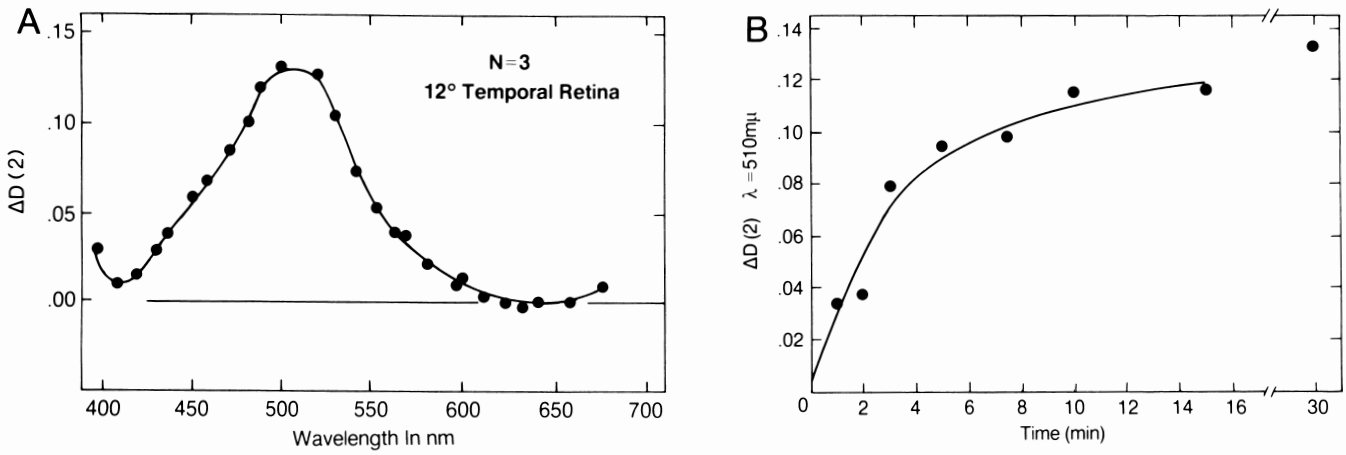

FIG 96–5.

A, Oguchi's disease. Fundus reflectometry shows a normal spectral response for the visual pigment rhodopsin. The patient was tested at 12 degrees temporal to fovea. The area under the curve reveals that a normal amount of rhodopsin is present in the area tested. **B,** fundus reflectometry shows normal visual pigment kinetics for rhodopsin, with regeneration 90% complete by 15 minutes and a half-time of regeneration of approximately 3 minutes.

chophysical, electrophysiological, and funduscopic abnormalities has yet to be given.

Fundus Albipunctatus

In 1910 Lauber[20] first defined this disorder and differentiated it from an ophthalmoscopically similar disorder, retinitis punctata albescens, one of the varieties of the progressive tapetoretinal degenerations. In his original paper he selected 25 cases from the literature and also described four of six children of a consanguineous marriage, all of whom had multiple small white spots in the retina that were associated with night blindness but no other visual defects. This differentiation from retinitis punctata albescens was thus made on the basis of the condition being stationary, the absence of any visual field changes, and the normalcy of the retinal vessels. Both disorders may be ophthalmoscopically similar in that there are a multitude of yellow-white spots located deep in the retina[10] that extend from the posterior pole, where they are most dense, to the periphery, where they are fewer in number. The macular area is invariably spared (Fig 96–6).

As one reviews the older literature, it is clear that there is marked disagreement as to what constitutes fundus albipunctatus and the relationship between this stationary problem and retinitis punctata albescens. These discrepancies were clarified when it was found that patients with the stationary form of the disease eventually do attain a normal dark-adapted final threshold if dark-adapted for a sufficiently long period[10] (Fig 96–7). Failure to fully adapt such patients may account for the findings in some reported cases of elevated dark-adapted thresholds in the absence of any other findings indicative of a generalized retinal degeneration.[11]

ERG findings were likewise variable and confusing until it was found that these responses were

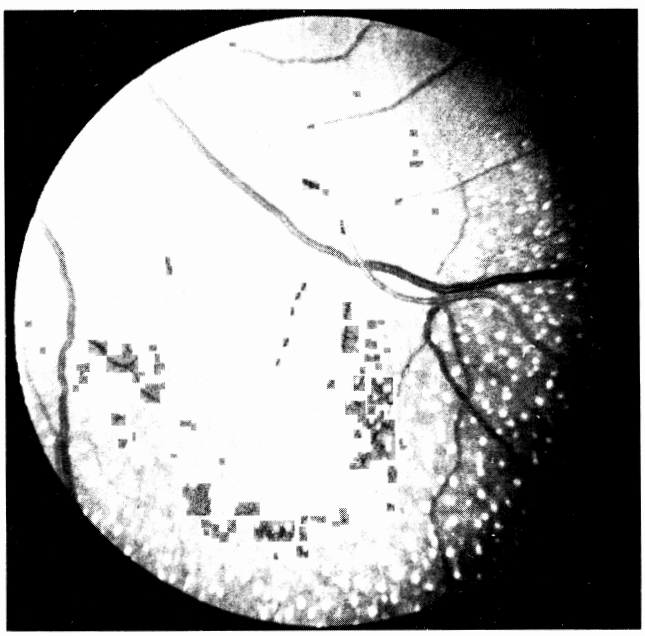

FIG 96–6.

Fundus albipunctatus. This fundus photo shows a multitude of yellow-white discrete spots scattered throughout the retina but sparing the macular area.

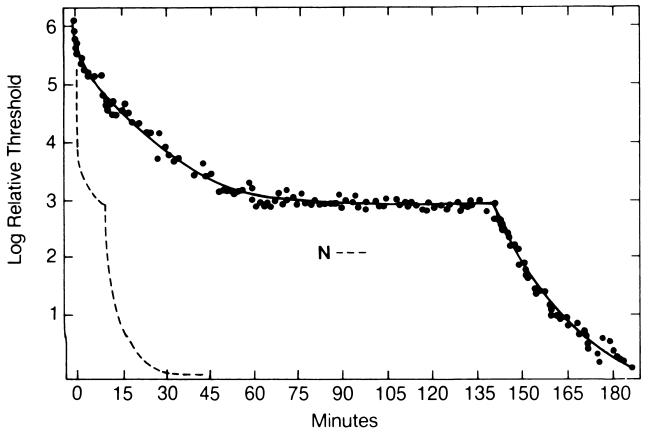

FIG 96–7.
Fundus albipunctatus: dark adaptation. Normal is illustrated by the *hatched line.* The patient *(closed circles)* shows a slow fall to a normal cone threshold and then a slow fall to the normal rod threshold.

also markedly delayed in attaining normal amplitudes[18, 31] (Fig 96–8).

The EOG likewise parallels the ERG, for a full EOG light rise will not be obtained until the patient with fundus albipunctatus has been dark-adapted

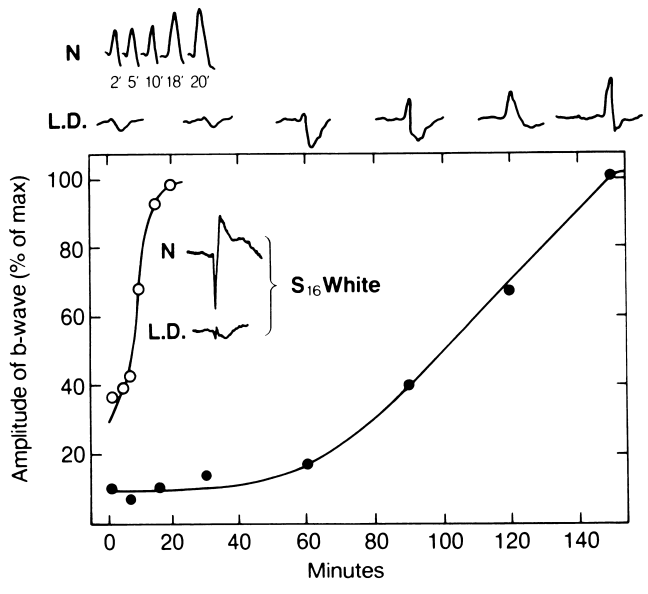

FIG 96–8.
Fundus albipunctatus: ERG amplitude response curve of a normal person *(open circles)* and a patient *(closed circles).* The values were derived from S_1 blue dark-adapted ERGs at various time periods as illustrated on top for the normal *(N)* and the patient *(L.D.).* Also noted is the 20-minute dark-adapted response to an S_{16} white stimulus for both the normal and the affected individuals.

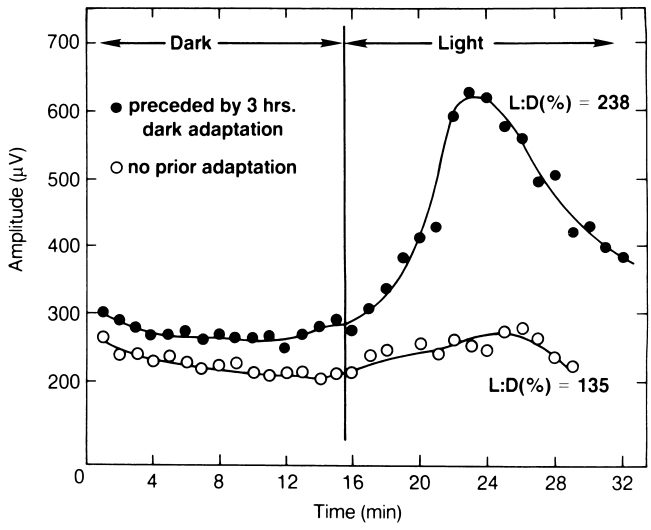

FIG 96–9.
Fundus albipunctatus: ERG amplitudes. With dark adaptation of 15 minutes *(open circles)* there is no EOG light rise. After an adaptation period of 3 hours *(closed circles)* the EOG light rise is normal.

for that period of time it takes to reach full dark adaptation (Fig 96–9).

These abnormalities were clarified by the studies of Carr and Ripps,[5] who demonstrated that the basic pathogenesis lay in markedly delayed regeneration of both the rod and cone visual pigments (Fig 96–10). Failure to recognize this marked retardation of visual pigment kinetics and the associated effect on retinal function, both electrophysiologically and

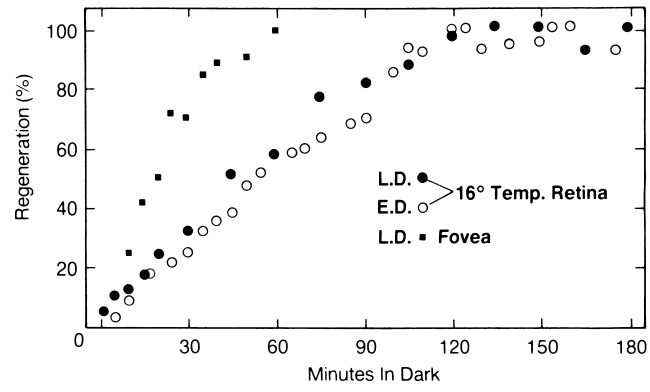

FIG 96–10.
Fundus albipunctatus: rate of regeneration of cone visual pigments *(closed squares)* and rhodopsin (*open* and *closed circles*) of patients L.D. and E.D. The normal half-time of regeneration of the cones is approximately 55 seconds (patient L.D. takes 20 minutes) and of the rods is approximately 3 minutes (patients L.D. and E.D. take 60 minutes).

psychophysically, serves to explain why past studies showed such widely variable findings.

The heredity seems most likely autosomal recessive, although Krill and Folk[18] describe a mother and son with the disease. The majority of reports, however, show a high incidence of consanguinity and a familial pattern most consistent with autosomal recessive inheritance.

A possible variant of this disorder was described by Kandori,[16] who termed it "fleck retina with congenital nonprogressive night blindness." In this disorder the fundus picture is different in that there are sharply defined flecks of yellowish color that are larger, more irregular in shape, and fewer in number than is seen in typical fundus albipunctatus. Electrodiagnostically the photopic ERG response was normal, while there was a delay in the generation of the scotopic response that paralleled the delay in dark adaptation,[17] findings very similar to what had been noted in some cases of fundus albipunctatus.

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