CONGENITAL STATIONARY NIGHTBLINDNESS*

BY *Ronald E. Carr,* MD

INTRODUCTION

CONGENITAL STATIONARY NIGHTBLINDNESS (CSNB) HAS BEEN A WELL-RECOGNIZED entity since 1838 when Cunier[1] described seven generations of a family in southern France with poor night vision but perfectly normal visual functions in all other respects. Later reports[2,3] verified and enlarged upon the original description of this family and subsequently several other forms of CSNB were described.

This disease entity can now be classified as follows:

I. CSNB: NORMAL FUNDI
   a. Autosomal dominant
   b. Autosomal recessive
   c. Sex-linked recessive

II. CSNB: ABNORMAL FUNDI
   a. Oguchi's disease
   b. Fundus albipunctatus

Although some authors[4,5] have considered such entities as drusen, flecked retina, and fundus flavimaculatus to be in the latter group, the electrophysiologic and psychophysical findings in these entities serve to easily separate them from those previously noted.

The purpose of this report is to discuss the various forms of CSNB, and on the basis of psychophysical and electrophysiologic studies to suggest the pathologic abnormality in each variety.

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HISTORICAL REVIEW

CSNB WITH NORMAL FUNDI.

One of the most complete genealogic records and one which perfectly exemplifies autosomal dominant inheritance is that known to have been established by Jean Nougaret who lived in the latter part of the 17th century. Nougaret was a butcher by trade and settled in the small French village of Vendémian, a town which maintained itself in isolation like so many similar small villages of that era. He was himself nightblind; had three similarly affected children, and the disorder was thereafter passed along from one generation to another in ever-increasing numbers. It was not until 1831 that one of Jean Nougaret's descendants came to the attention of the scientific community. At that time a 23 year old boy, who was a 5th generation descendant, was excused from military service because of his inability to see at night. The Military Surgeon of Montpellier, from whose district this boy had been conscripted, contacted Florent Cunier, a Belgian ophthalmologist. He told him of this individual's problem as well as the fact that there were living members of three preceding generations who had similar problems. Cunier traced the genealogic tree, found Jean Nougaret the common ancestor, and published his findings which covered seven generations and included 86 persons afflicted with nightblindness.[1]

In the early part of the 20th century this disorder attracted the attention of Nettleship, and with the assistance of Dr. H. Truc, Professor of Ophthalmology at the University of Montpellier, as well as M. Capion, curé of Vendémian, he published a continuation of the genealogy of Cunier and confirmed his findings.[2] This study, carried up to 1907, encompassed nine generations, included 2121 persons of whom 135 were nightblind, and enabled Nettleship to state that these were truly cases of stationary nightblindness and not of a progressive nature. An attempt to further update this family was made in 1949[3] but the two World Wars and changing lifestyles led to the dissolution of the original genetic isolate. The name Nougaret still lives on, however, for in Europe this form of dominantly inherited CSNB is referred to as the "Nougaret variety".

CSNB without fundus changes can also be inherited as an autosomal recessive or as a sex-linked recessive, both of these varieties often being associated with myopia. In 1855 Donders[6] reported the sex-linked variety of this disease in his study of congenital retinal disorders, and in 1925 Varelmann[7] collected 12 such families from the literature and added one of his own.

In 1925 Gassler[8] first reported this syndrome transmitted as an autosomal recessive and a recent paper by Merin and associates[9] fully discusses the clinical and electrophysiologic findings in 32 patients (25 families) in whom the heredity was both autosomal recessive and sex-linked recessive. While the association of myopia and CSNB is invariably found in the sex-linked type of heredity, the autosomal recessive variety does not always show this combination. It is of interest that in those patients with the combined disorders there is a high association of poor visual acuity, strabismus, and nystagmus.

The initial psychophysical studies of CSNB without fundus changes were performed by Dieter[10] who substantiated the clinical impression of that time of selective rod impairment. He studied dark adaptation in three subjects and found no rod-cone break but a curve indicative of cone function alone. This was confirmed by Kotuka,[11] but Garabédian and Meunier[12] found somewhat different functions in another patient. They demonstrated the initial (cone) segment of the dark adaptation curve to be slightly elevated, and while there was evidence of a bipartite curve, there was no adaptation below the cone level. This would indicate an abnormality of both rod and cone function, a theory that was subsequently proven to be correct.

With the advent of clinical electroretinography the groundwork was laid for a better understanding of these disorders. Although Bjork and Karpe[13] published the ERG findings in two cases of supposed CSNB in 1951, on closer study of the data these patients appear instead to have generalized retinal degeneration. The first authentic case of CSNB to be studied electrophysiologically was that of Schubert and Bornschein[14] in 1952. They demonstrated an apparent absence of the scotopic b-wave although there was a progressive increase in the size of the initial a-wave during dark adaptation. This "negative ERG" in CSNB was confirmed in other reports[15,16] but in 1953 Carroll and Haig[17] showed an entirely different sort of response associated with CSNB. In a well-documented pedigree of autosomal dominant heredity, electrophysiologic studies demonstrated a reduced but normal-appearing photopic response which underwent a slight increase under scotopic conditions but essentially retained its photopic character. Riggs, who had done these ERG studies, separately published this case and two others the following year.[18] Similar responses were gotten by François et al[19] who were able to study three descendants of Jean Nougaret. The mild controversy as to whether there were two different ERG responses in CSNB was resolved by Armington and Schwab[20] who clearly showed both forms in patients with this disease. Interestingly, the mode of transmission in both of their patients was autosomal recessive, thus

showing that the ERG response was not specific to a particular hereditary pattern, a point well-illustrated in a more recent study by Auerbach et al.[21]

In 1957 Goodman and Bornschein[22] published an excellent study of the ERG responses in a patient with the negative-type ERG response and clearly showed that the negative response increased during dark adaptation, evidence that this variety of CSNB shows scotopic function on an electrical basis although by other parameters there was seemingly a near-absence of scotopic function. While these authors felt that this might be evidence of a pathologic abnormality in the distal segments of the rod receptors, this was not borne out by the sole histologic study which was done. In 1963 Babel,[23] received the eyes of a subject who was a member of a family with the dominant form of CSNB previously studied by Latte.[24] Aside from somewhat weak staining of the photoreceptor outer segments with the MacManus stain, the remainder of the microscopic study was normal. A second histologic study, reported in this same paper, is open to doubt since the patient had one brother affected with retinitis pigmentosa.

A series of papers by Carr and co-workers[25-28] served to more clearly elucidate the possible abnormalities in this disease. Utilizing fundus reflectometry in order to study the kinetics of the visual pigments *in vivo* as well as electroretinography, electro-oculography, and studies of spatial integration, the authors were able to demonstrate that these particular forms of CSNB were probably due to defects in neural transmission, occurring in one variety in the region of the inner segments of the photoreceptors and in the other variety in the region of the bipolar cells. This localization clearly demonstrated that these forms of CSNB were neither due to abnormalities of rhodopsin metabolism, as had previously been surmised,[29,30] nor related to higher center dysfunctions. This work was subsequently confirmed in two separate studies. Auerbach and associates[21] studied 95 patients with both autosomal recessive and autosomal dominant varieties of CSNB. They concluded that scotopic activity could be demonstrated by the ERG as well as by spectral sensitivity studies, that photopic activity was likewise subnormal, and that there was no consistent relationship between either of the two types of ERG waveform and the hereditary pattern. These authors showed that several of their cases were very slowly progressive. Alpern and associates,[31] utilizing the pupillomotor response during the course of dark adaptation, demonstrated that rod bleaching signals were normal even though there was no functioning rod vision; further evidence that the defect in some forms of CSNB could be post-receptoral.

Carr and co-workers[26] investigated cone function in this same group of patients and found that the concentration and kinetics of cone visual pigments were likewise normal; a finding also noted by Alpern and his associates.[31] They also confirmed what had been noted briefly by previous authors;[17,18,19,20,22] namely, that photopic function like scotopic function also was impaired. This point was later emphasized by Krill and Martin[32] who studied photopic function in 14 patients with CSNB and found varying abnormalities of the cone system in all patients.

CSNB WITH ABNORMAL FUNDI: OGUCHI'S DISEASE.

In 1907 Oguchi[33] described an unusual form of CSNB which was characterized by a peculiar grey-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 maculas appeared abnormally dark in contrast to their surrounding. He presented this entity in greater detail in 1912[34] 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[35] 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. After exposure to light the retina then slowly reverted back to its original metallic color.

Up until 1931 over 60 cases were described, all in the Japanese literature. However, Scheerer[36] then reported the first case in Europe and eight years later Klein[37] discussed the first case seen in the United States. Following this it was evident from the scattered reports that this rare disorder was indeed world-wide.

The autosomal recessive mode of inheritance of this disorder was evident even in Oguchi's original cases[34] where consanguinity was known in two of the three pedigrees. This was confirmed in the large study of Takagi and Kawakami[38] who presented three of their own cases and reviewed the 56 cases described up to that time and found the incidence of consanguinity to be 62%. Falls,[39] on the other hand, felt there was evidence of partial sex-link inheritance based on the discrepancy of affected males and females.

While the abnormal fundus coloration served to distinguish this variety of CSNB from other forms, the psychophysical course of dark adaptation was likewise found to be very different. Both Nakamura[40] and Yamanaka[41] demonstrated that following prolonged adaptation most of the patients showed a slow fall in thresholds until normal levels were reached.

The time was variable, ranging from two 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 Mizuo's phenomenon and a slow fall in adaptation; Type II A showed Mizuo's phenomenon but no change in adaptation from the cone threshold; and Type II B showed no Mizuo's phenomenon and no change in adaptation. These latter types thus showed dark adaptation curves similar to what is seen in CSNB without fundus changes. Kawakami[42] confirmed these variants, and in one type (II-A) Doeschatte and co-workers[43] found an abnormality in the cone threshold also, similar to other varieties of CSNB. During the course of these early studies[40,42] it was recognized that Mizuo's phenomenon was not related to threshold change, a finding which was subsequently confirmed in later, more detailed studies.[44,45]

The first electrodiagnostic investigations of Oguchi's disease were carried out by Hirose[46] who demonstrated an absent b-wave. Other authors[47,48,49] confirmed this, and in 1965 Carr and Gouras[44] presented a detailed ERG analysis of the disease. Utilizing a standard clinical recording technique they found the photopic response to be essentially negative. On dark adapting their patients for a period of 10 minutes there was some deepening of the a-wave but no large positive scotopic response, only a small response similar in type and peak latency to that seen under photopic conditions. Even after 24 hours of dark adaptation there was no scotopic increment in spite of the fact that the dark adapted threshold had reached normal levels. To further elucidate the ERG pattern during this period of normal thresholds, computer summation techniques were used. By the use of a low intensity red light, selected so as not to adapt the patient, Carr and Gouras found a normal cone response but an abortive rod response which was both reduced in amplitude and markedly increased in latency. While this kind of ERG activity is seemingly most typical in Oguchi's disease, Nagata[50] found some evidence of scotopic return after 10 minutes of adaptation, and Berson[51] has even noted a normal scotopic response to a single flash following 24 hours of dark adaptation.

Because of the 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.[43,47,52] However, the study of Carr and Ripps[45] which measured *in vivo* the concentration and kinetics of the visual pigments in a case of Oguchi's disease, proved this not to be the case. In a full series of

psychophysical and electrophysiologic studies they showed that rhodopsin was normal in both amount and regenerative properties and also that rhodopsin photosensitivity was normal. It thus appeared that this disease, like CSNB with normal fundi, was related to an abnormality of neural transmission.

An attempt to define the pathologic abnormality in Oguchi's disease has been made dating back to Yamanaka[41] and Oguchi[53] in the mid 1920s. The former had the first opportunity to do histologic 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. Oguchi described a compact arrangement of cone nuclei, an unusual distribution of cones which extended out 20 degrees temporally from the disc, a dense pigment epithelium with an abundance of fuscin granules, and an additional layer of granular pigment interspersed between the photoreceptors and the true pigment epithelium. Yamanaka found no such additional layer and considered the abundance of round-shaped fuscin granules and their confinement to the apical portion of the pigment cells the characteristic feature. It was not until 40 years later, in 1963, that Kuwabara and associates[54] had the opportunity to study another eye with this disease. In this excellent histopathologic and electron microscopic study several findings were noted. The authors confirmed 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 pathologic but 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 a normal 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. There was no abnormal cone distribution in the retina in contrast to Oguchi's findings.[53] A more recent histologic study by Yamanaka[55] is open to question in that both parents of the affected individual had retinitis pigmentosa and the individual had reduced vision and retinal pigmentary changes. The abnormal retinal reflex described by the author may have been related to the pigment epithelial changes which occur in the tapeto-retinal degenerations[56] and not be related to Oguchi's disease.

CSNB WITH ABNORMAL FUNDI: FUNDUS ALBIPUNCTATUS

In 1910 Lauber[57] first defined this disorder and differentiated it from an ophthalmoscopically-similar disorder, retinitis punctata albescens, one of

the varieties of the progressive tapeto-retinal degenerations. In his original paper he selected 25 cases from the literature and also described four of six children of a consanguinous marriage in whom there were multiple small white spots seen in the retina and associated with nightblindness 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 are ophthalmoscopically-similar in that there are a multitude of yellow-white spots, located deep in the retina[58] and which extend from the posterior pole, where they are most dense, to the periphery where they are less in number. The macular area is invariably spared. The size of the spots is quite constant and Fuchs[59] described them as the size of a second order arteriole.

While Lauber felt that there was a sharp differentiation between the two varieties with certain intermediate forms also present, other authors[60] consider the two disorders as being similar in type and varying only in expression and development. This is based on the following pieces of evidence; first, that the two disorders appear similar ophthalmologically; second, that there are some cases of retinitis punctata albescens which are very slowly progressive;[61,62] and third, the presence of several genealogies in the literature in which there is an association of both disorders in different family members.[63,64] Giannini,[65] however, considered the disorder one of the group of stationary nightblindness, similar to Oguchi's disease, and separate from the progressive variety.

The similarity to Oguchi's disease is most manifest when dark adaptation is tested, for normal thresholds are reached only after time periods of 40 minutes[66,67] to several hours.[58,64,68] Failure to fully dark adapt except after long periods 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 degeneration.[69] Like other varieties of CSNB cone function has also been noted to be affected.[64,67]

Electroretinographic findings have been widely variable. Franceschetti and Dieterle[69] noted that the dark adapted ERG could be perfectly normal in spite of elevated dark adaptation levels, and this dichotomy between ERG and adaptation was also noted by François et al[47] and again in a later publication by Franceschetti and Dieterle.[70] Smith and associates[67] and Krill and Folk,[66] however, found that ERG responses followed the course of dark adaptation such that there was a delay in reaching the full amplitude of the b-wave response which paralleled the delay in subjective dark adaptation. Failure to follow the course of adaptation with the ERG may account for the finding of Franceschetti and

co-workers[60,64] of a markedly reduced ERG response in patients with the fundus albipunctatus.

The heredity seems most likely autosomal recessive although Krill and Folk[66] 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[5] and entitled "fleck retina with congenital non-progressive night blindness". In this disorder the fundus picture is different in that there are sharply defined flecks of yellowish color which are larger, more irregular in shape, and fewer in number than seen in typical fundus albipunctatus. Electrodiagnostically the photopic ERG response was normal while there was a delay in the generation of the scotopic response parallelling the delay in dark adaptation,[71] findings very similar to what had been noted in some cases of fundus albipunctatus.

MATERIALS AND METHODS

SUBJECTS

A total of 18 patients with various forms of CSNB were studied. The distribution was as follows:

I. *Normal Fundi without myopia (one patient).* This subject, a 25 year old woman was from a family whose members inherited nightblindness as a dominant trait. Confirmatory examinations were made elsewhere of her father, two sisters, her two daughters, and two nieces and substantiated the diagnosis of an autosomal dominant variety of CSNB. Her visual acuity was 20/20 bilaterally and the fundus exam was normal.

II. *Normal fundi with myopia (13 patients)* Ten males and three females were in this group. The exact hereditary pattern could not be established for any of the males although two of the patients were brothers. However, in no case was there any antecedent family member with the disease by history or on examination. All affected females were presumed to have the disorder as an autosomal recessive. Only three of the patients had normal visual acuity, the remainder varying from 20/30 to 3/200. The degree of myopia in spherical equivalents ranged from −2.00 to −14.00 diopters with a median of −6.00 diopters. Nystagmus was present in three subjects, strabismus in four, and one patient had an external ophthalmoplegia. While all of the patients showed peripapillary changes

compatible with their degree of myopia, ten also demonstrated excessive granularity of the macular area.

III. *Abnormal fundi: Oguchi's disease (two patients)* A male (age 14) and a female (age 18) both had complaints only of poor night vision. The female patient had a similarly affected sister reported elsewhere.[44] Visual acuity in both patients was 20/20 bilaterally and the ophthalmoscopic abnormalities associated with Oguchi's disease were similar (Figure 1). When the fundus was first examined, a metallic silver-gray sheen that originated deep to the retinal vessels was seen in the midperiphery of both eyes. Following prolonged dark adaptation, the metallic reflex disappeared and fundus color was entirely normal (Mizuo's phenomenon). After about 15 minutes in moderate room illumination, patches of gray began to reappear in the midperiphery and extended over this entire region after one hour. Noteworthy was the sparing of the posterior pole and the more peripheral retinal regions, which remained free of any visible discoloration, even after exposure to very high luminances.

IV. *Abnormal fundi: Fundus albipunctatus (two patients)* The two subjects were brothers, ages 42 and 44, born on the Dutch island of Saba. Although there was no history of parental consanguinity, there was the likelihood that some inbreeding had occurred in former generations. Both subjects were aware of difficulty seeing at night, but felt that this problem was minor since visual perfor-

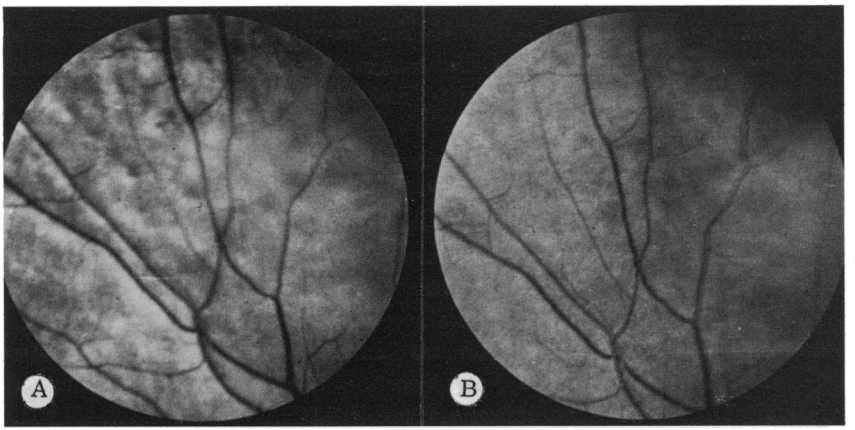


FIGURE 1
Oguchi's disease. Fundus photographs illustrating the color change in the retina (Mizuo's phenomenon), A. before adaptation and B. after 4 hours adaptation.

mances tended to improve if they remained in darkness for an hour or two. Their parents and two sisters were said to have normal night vision. On routine ophthalmological examination, both subjects had similar findings. Visual acuity was 20/20 after correction of a small refractive error, and with the exception of the fundus appearance, all other routine tests were within normal limits. Ophthalmoscopically, their fundi showed an array of whitish punctate opacities encircling the posterior pole and situated deep to the retinal vessels. These spots were in greatest concentration out to the equator and then thinned rapidly in the periphery. The macular areas were spared (Figure 2).

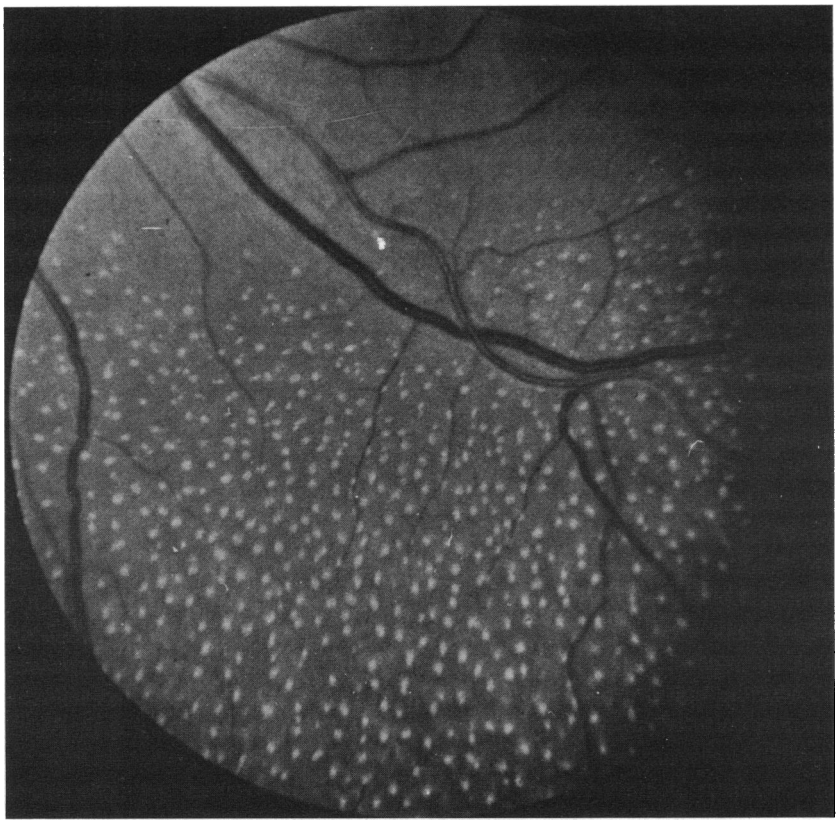


FIGURE 2
Fundus albipunctatus. Fundus photograph showing a band of discrete yellow-white spots encircling the macular area.

DARK ADAPTOMETRY

Testing was performed monocularly on a modified Goldmann-Weekers Adaptometer after the subject's pupils had been dilated with 10 per cent phenylephrine hydrochloride (Neosynephrine) and 1 per cent cyclopentolate hydrochloride (Cyclogyl). Prior to an experimental run, the subject was light adapted for seven minutes to a luminance of 8,900 candela per square meter. Thresholds during dark adaptation were measured for a white, circular testfield subtending 4.5 degrees at the subject's cornea and located 12 degrees in the nasal visual field (temporal retina). Test flashes were 0.7 second in duration.

ELECTRORETINOGRAPHY

Standard electroretinal responses were elicited with 10 μsec flashes of white light from the Xenon discharge lamp of a Grass photic stimulator. The open end of the lamp housing was covered with opal glass to give a uniformly illuminated field subtending a visual angle of 25 degrees. The control circuit of the stimulator permitted variation in flash luminance from about 4.3×10^6 to 6.8×10^7 cd per square meter in steps of approximately 0.3 log unit. Although the spectral characteristics of the flash vary somewhat between settings, this was not considered an important factor in these tests. Both flicker and single-flash stimulation were employed in an attempt to evoke photopic and scotopic responses, respectively. Electroretinograms were recorded as the potential change between a contact lens electrode (Burian-Allen) and a reference electrode adherent to the subject's forehead. The potentials were amplified and recorded on an ink-writing polygraph (Grass Instrument Company). The frequency response of the system was set for 3 db attenuation at 0.6 and 60 cycles per second.

In studying cases of Oguchi's disease a computer of average transients (CAT) was used to summate responses to repetitive, dim red light stimuli. This was utilized in order to elicit ERG responses without altering retinal dark adaptation. The flashes were from a Grass stroboscope and presented every four seconds. The energy in wavelengths greater than 580 nm was considerably reduced by means of an absorption filter and the overall energy in the stimulus was dim enough not to interfere with the dark adapted state of the subjects.

ELECTROOCULOGRAPHY

The electrooculographic technique described by Arden and Kelsey[72] was used to determine the effect of light on the corneofundal potential. Chlorided silver electrodes were affixed to the subject's skin near the

lateral and medial canthi of each eye. The electrodes led to a differential amplifier (time constant = 1.5 second), the output of which was recorded on an ink-writing oscillograph. The subject was required to fixate alternately two small neon lamps located in the horizontal plane and separated by an angle of 40 degrees with respect to the eye. The lamps were electronically controlled to provide sequential flashes every 0.8 second. Eye movements were recorded every minute for a period of about 10 seconds under the following conditions: (a) during a 10 minute practice session at an ambient room illumination of 120 cd per square meter, (b) in complete darkness for 15 minutes, and (c) during a 15 minute period during which the eyes were exposed to a luminance of 8,900 cd per square meter. As fixation was moved from one lamp to the other, the positive corneal potential was applied to each electrode in turn. Measurements were made of the response amplitudes resulting from a complete horizontal saccade. The average of five such readings at each one-minute interval was taken as the value of the standing potential. The minimum potential in darkness (the dark trough) and the maximum potential during light adaptation (light peak) were measured and the ratio of light peak to dark trough were determined from these data. A ratio of 180% or greater was considered normal.

FUNDUS REFLECTOMETRY

The type apparatus used is shown schematically in Figure 3. A Xenon arc lamp, operated at constant current from a stabilized direct current power supply, provided the source (S) for both reflectivity measurements and bleaching. Light for the measuring beam passed through a heat filter (C_1), was focused by lens L_1 upon a small circular aperture A_1, and then collimated by lens L_2. The beam then traversed, in turn each of twenty-six narrow band interference filters (399 mμ to 676 mμ) mounted in spectral order on the wheel (W) driven at a rate of 2 revolutions per second. The beam was directed into the subject's eye by a prism (P_1). With sliding mirror M removed from the optical path, lens L_3 formed an image of aperture A_1 in the plane of the subject's dilated pupil. Aperture A_2, conjugate with the subject's retina, restricted the dimensions of the beam to a visual angle of 1 degree, 44 minutes. Depending upon the position of a small fixation spot, the test region could be foveal or at any desired location in the peripheral retina.

Light reflected from the fundus and emerging through the upper half of the pupil was reflected by prism P_3 to lens L_6 which focused the rays onto aperture A_5. The latter corresponded in area to the retinal image of the test field and served to eliminate much of the stray light from planes not

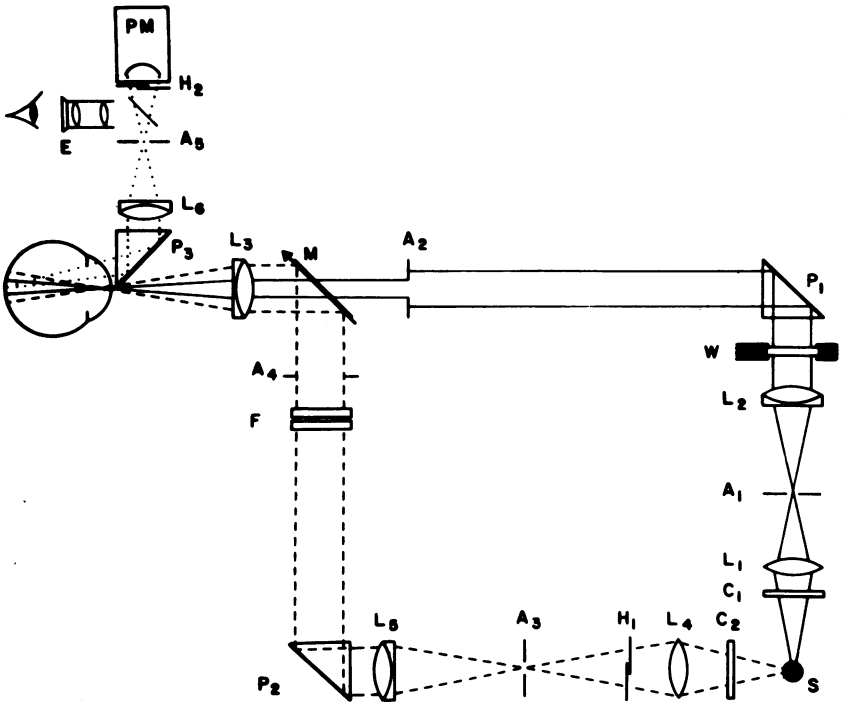


FIGURE 3
Schematic diagram of the apparatus for fundus reflectometric measurements (not to scale). The collecting system has been turned 90 degrees to show its components. See text for details.

conjugate with it. Accurate centration was assured by observation through eyepiece E which gave a magnified view of the subject's fundus and overlying test field. The light then fell on the cathode of a photomultiplier (PM), the output of which was fed through an operational amplifier both for display on a direct-coupled oscilloscope and computer processing. For bleaching, the alternative optical path of Fig. 3 was used. With shutter H_1 opened, and mirror M in the position shown, the measuring beam and photomultiplier were occluded by shutter H_2 and the bleaching light entered the eye after reflection at prisms P_1 and P_2. The aperture A_4 restricted the angular subtense of the bleaching field at the eye to an angle of 4 degrees, 35 minutes in diameter. The intensity and spectral composition of the beam could be varied by filters at F. The remaining optical elements of the system were shared with the measureing beam.

The procedure was such as to obtain complete spectral scans of the test region, first with the eye fully dark adapted, and again after it had been exposed to an intense bleaching light for 30 seconds. For each measuring wavelength, the changes in density Δ D (2), that is, the density changes corresponding to light traversing the retina twice, were then computed from measurements of the corresponding oscilloscope deflections. This operation was performed for every waveform of 8 successive spectral scans taken during the test period. The rate at which the bleached photopigments regenerated was obtained from reflectivity measurements taken at various times after the bleaching light was extinguished. Dependent on the pigments being studied (that is rod or cone), plotting the values of Δ D (2) near the maximum of the difference spectra during the course of dark adaptation gave the time course of regeneration.

All data processing was performed on-line either by a Control Data Corporation 160-A digital computer linked by Western Electric Data Phones or by a PDP-8I digital computer. The area of each waveform was calculated and used in the determination of the difference spectrum.

RESULTS

NORMAL FUNDI WITHOUT MYOPIA

The results of dark adaptometry (Figure 4A) demonstrated an absence of the normal bipartite form of the curve as is found in the normal extrafoveal retina. Thresholds fell rapidly at first, paralleling the normal curve but then reached a final threshold which was maintained throughout subsequent testing. This foveal level was approximately 0.5 log units above the normal cone plateau and approximately 3 log units above the normal fully-adapted rod level. Even after 24 hours of patching, the threshold was unchanged. The absence of any discontinuity in the curve, suggestive of a rod-cone break, indicated that not only is the entire adaptation process due to the cone system, but that even the cones are not as sensitive as in the normal.

Electroretinography (Figure 4B) bears out this loss in cone sensitivity and absence of any rod components. In comparing these responses with those of a normal individual, it was evident that even a very intense flash under fully dark-adapted conditions gave only a much reduced photopic-like potential. This reduction in potential was also noted under photopic conditions in which the flicker response, indicative of cone function alone, was seen to be severely depressed.

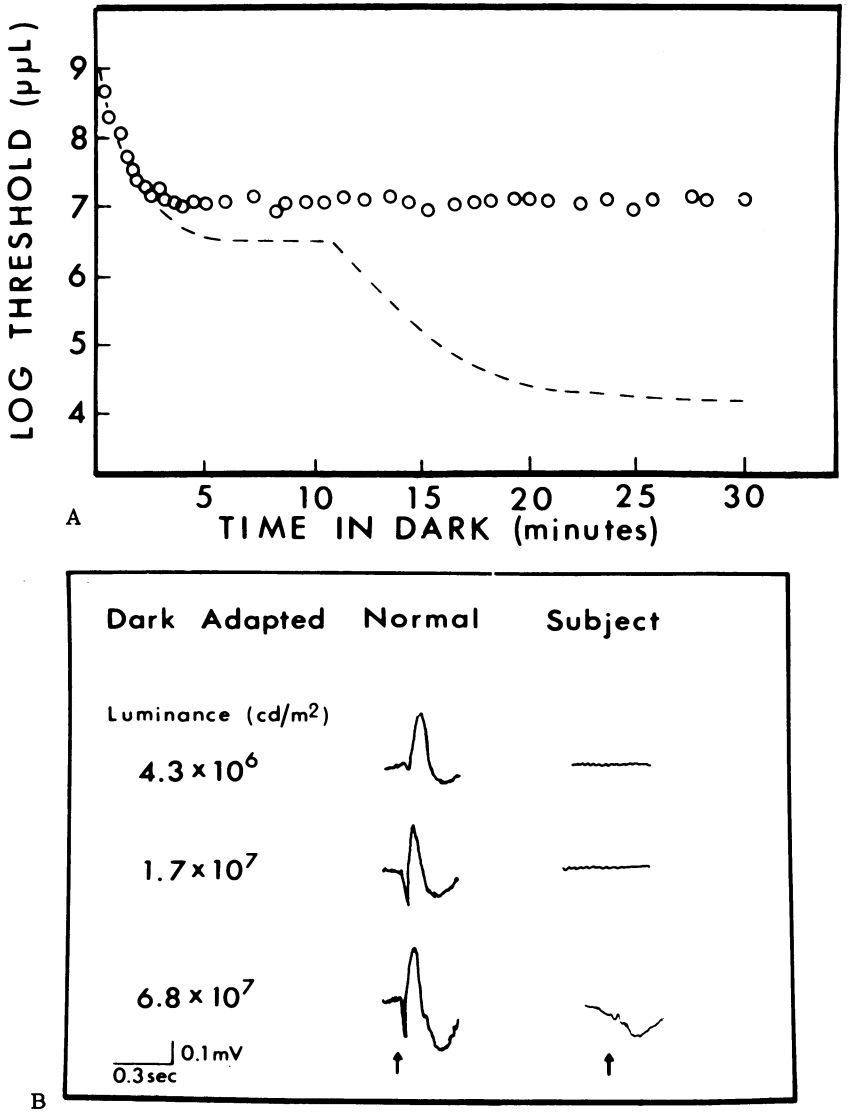


FIGURE 4

A. Normal fundi without myopia. Course of dark adaptation following 7 minutes exposure to a luminance of 8900 cd per square meter. Data are for a 4.5 degree test field located 12 degrees nasal to fixation. The dashed line represents the normal function for equivalent test conditions.

B. Normal fundi without myopia. Electrical responses elicited in the dark adapted eye at three levels of flash intensity.

Electrooculography (Figure 5A) demonstrated a marked reduction in the EOG light rise as compared with the normal. Normal values are greater than 180% in equating the light peak to the dark trough. This subject showed a light rise of only 130%, a ratio which can be seen in normal base-line fluctuations under invarient conditions of illumination.

Figure 5B demonstrates the difference spectra measured in the parafoveal retina, the same region used for dark adaptometry. The maximum density change occurred at 510 mμ, attesting to the fact that rhodopsin was present in the retina, and in terms of magnitude and spectral position the results were comparable to those of normals.[73, 74]

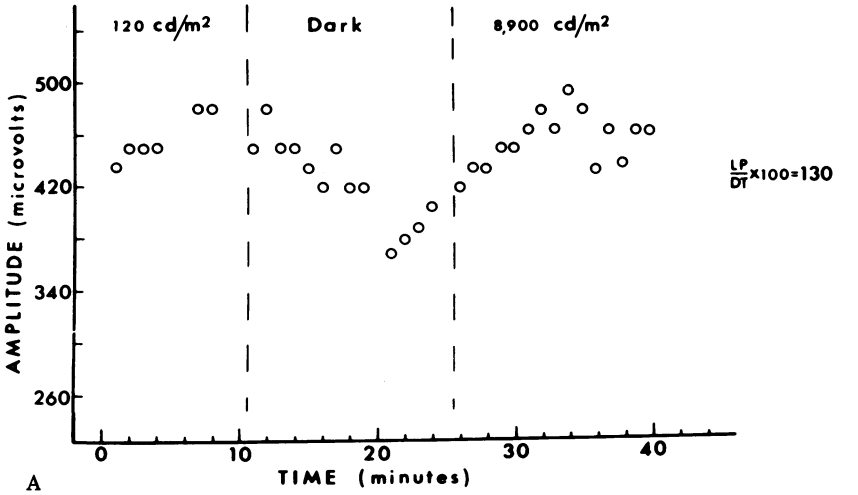
Regeneration data obtained after exposure to an intense bleaching light are noted in Figure 6A. The data points represent the course of visual pigment regeneration as measured at λ = 510 mμ from the density difference spectra obtained at various times during the course of dark adaptation. The rate of regeneration with a half-time of 3 minutes agrees with the normal.[75]

NORMAL FUNDI WITH MYOPIA

Psychophysical and electrophysiologic studies in this group of patients were similar in type and the results presented are those of an 18 year old male with 20/20 corrected acuity. The refractive error was −4.00 OD and OS and there was no nystagmus or strabismus.

Dark adaptometry (Figure 6B) is again compared with the normal bipartite curve. Unlike the previous subject the initial rate of adaptation was slower but sensitivity continued to increase over a longer time period. Also, the thresholds did not follow a strict monophasic time course, but a discontinuity in the curve at 15 minutes suggested a "rod-cone break", that is, a transition from cone to rod vision. Assuming that this is a changeover point, this subject then also showed not only defective rod function, but also an abnormality in cone function.

Electroretinography (Figure 7A) demonstrated markedly different responses from the above-noted group. Under dark adapted conditions a weak stimulus (4.3×10^6 cd/m^2) gave a response in which the initial a-wave was similar to the normal but the b-wave was grossly reduced in amplitude. As the flash luminance was increased only the a-wave increased in amplitude while the b-wave remained small. The a-wave response was equal in amplitude to that of the normal. Examination of the cone system by the use of flicker ERG demonstrated a slight reduction in amplitude as compared to the normal.



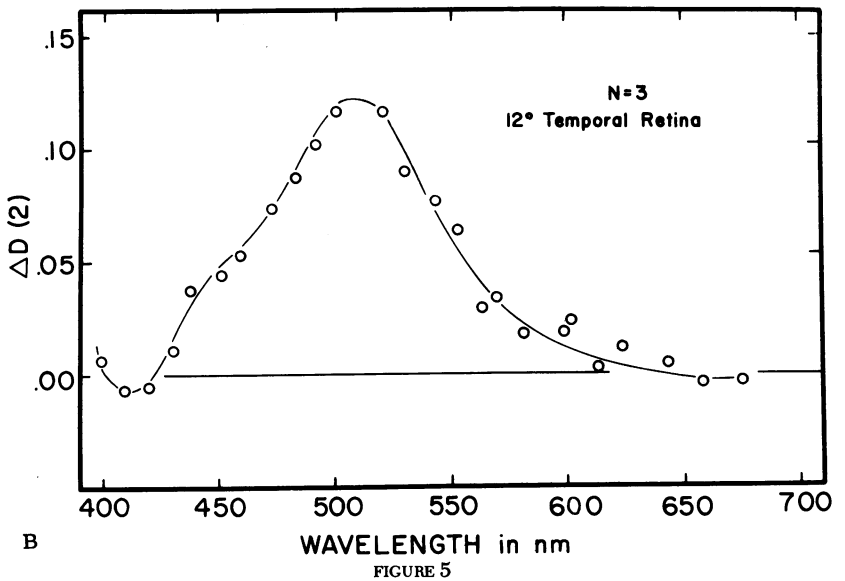


FIGURE 5

A. Normal fundi without myopia. Electrooculograms recorded at three levels of retinal illumination. Each point represents the average of five pen swings in microvolts. The rise in potential at the highest luminance level is given as a ratio of the light peak to the dark trough. A normal ratio is 180 percent or greater. B. Normal fundi without myopia. Difference spectra measured at 12 degrees in the temporal retina. A white bleaching light of 7.5 log troland seconds was used. The ordinate Δ D(2) gives the density change for double transit through the retina; density losses due to bleaching are plotted as positive values. A best fit line is fitted to the data point.

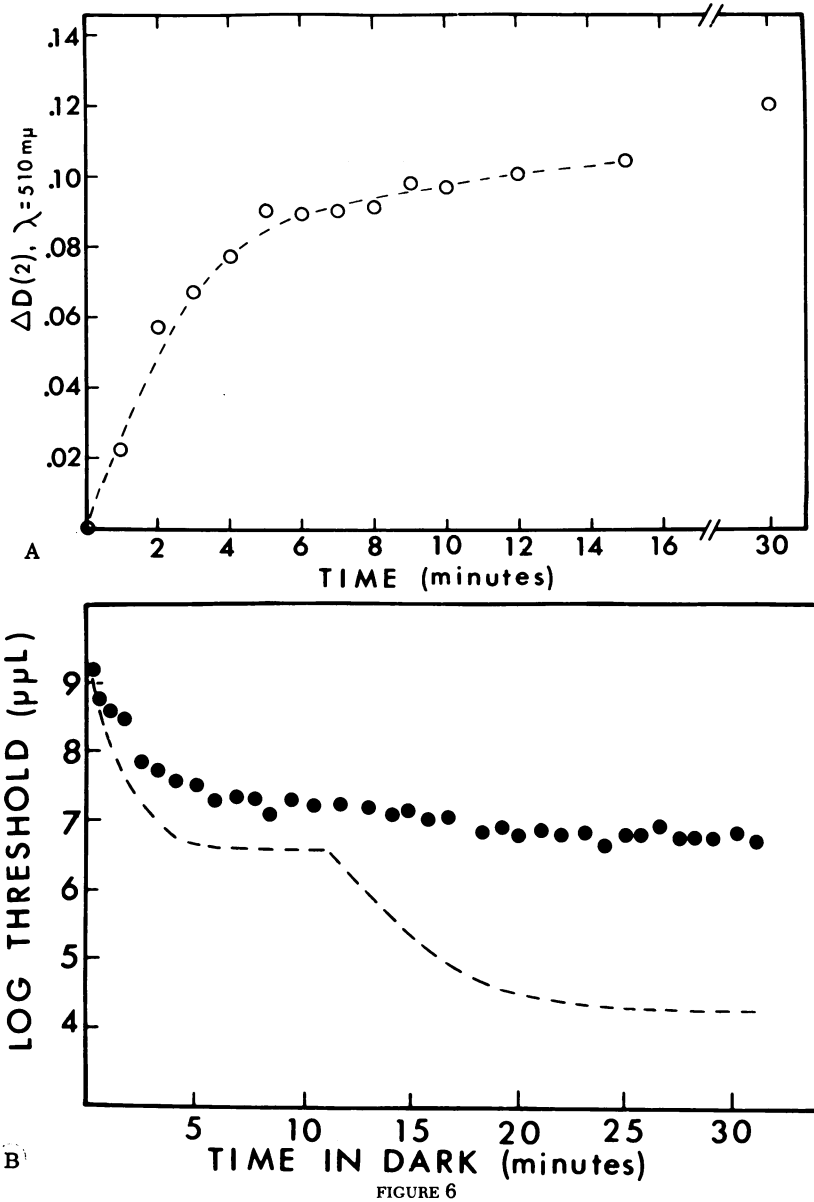
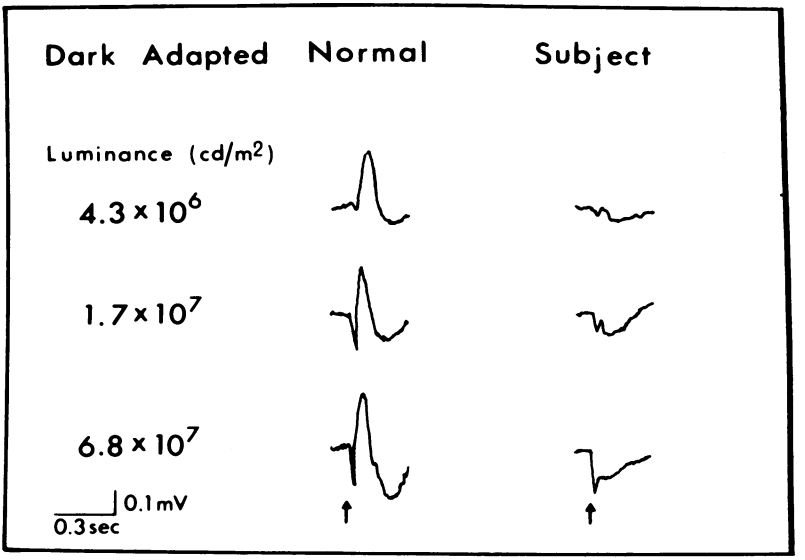
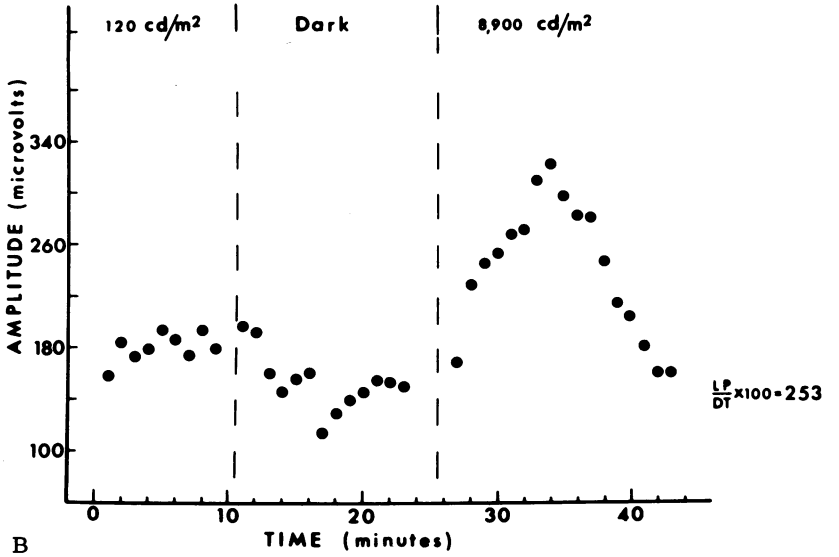


FIGURE 6

A. Normal fundi without myopia. Regeneration of rhodopsin. Measuring wavelength was 510 nm. B. Normal fundi with myopia. Course of dark adaptation following 7 minutes exposure to a luminance of 8900 cd per square meter. Data are for a 4.5 degree test field located 12 degrees nasal to fixation. The dashed line represents the normal function for equivalent test conditions.



A



B

FIGURE 7

A. Normal fundi with myopia. Electrical responses elicited in the dark adapted eye at three levels of flash intensity. B. Normal fundi with myopia. Electrooculograms recorded at three levels of retinal illumination. Each point represents the average of five pen swings in microvolts. The rise in potential at the highest luminance level is given as a ratio of the light peak to the dark trough. A normal ratio is 180 percent or greater.

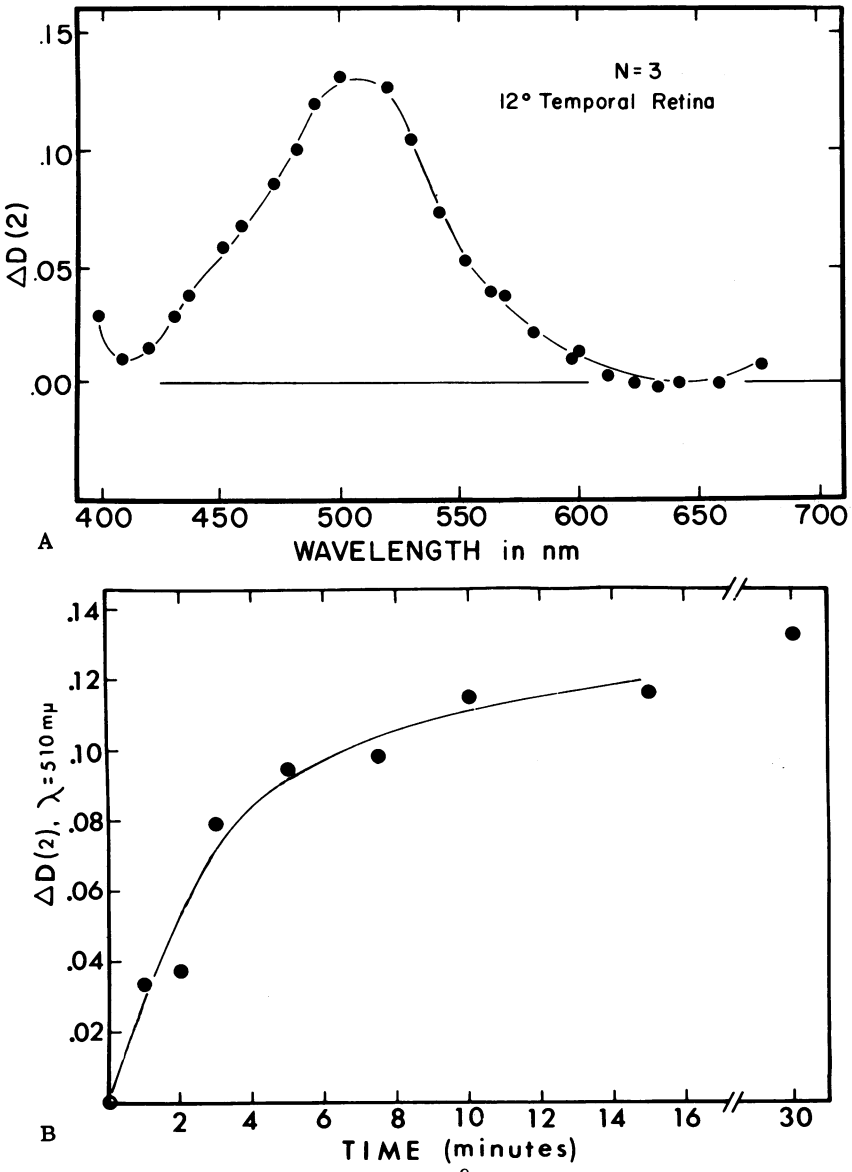


FIGURE 8

A. Normal fundi with myopia. Difference spectra measured at 12 degrees in the temporal retina. A white bleaching light of 7.5 log troland seconds was used. The ordinate Δ D(2) gives the density change for double transit through the retina; density losses due to bleaching are plotted as positive values. A best fit line is fitted to the data points. B. Normal fundi with myopia. Regeneration of rhodopsin. Measuring wavelength was 510 nm.

The electrooculogram (Figure 7B) showed a normal light rise, the lower level of normalcy being 180% in comparing the light peak to the dark trough.

Difference spectra (Figure 8A) and regeneration data (Figure 8B) showed that not only was rhodopsin present in the retina of such patients but it was normal in concentration, spectral position, and kinetics.

ABNORMAL FUNDI — OGUCHI'S DISEASE

Dark adaptometry (Figure 9) is markedly different from the preceding varieties CSNB. In order to encompass the entirety of the dark adapting process the results are presented on a compressed time scale. Cone adaptation proceeded normally and reached a plateau in about 10 minutes. But unlike the normal, in which rod adaptation was complete by 30 minutes, there was no evidence of rod function until 2 hours of dark adaptation had passed. At this point there was a very slow fall over another 2 hours before normal final thresholds were obtained.

Electroretinography (Figure 10A) showed a normal photopic response to both single stimuli as well as with flicker. The scotopic response following a normal period of adaptation showed a predominantly negative response with no positive increment. This initial negative response was no larger then that seen under photopic conditions; evidence that there was essentially no rod contribution after this period of adaptation. The absence of a rod contribution was demonstrable by the use of a monochromatic red stimulus; a wavelength which in the normal easily demonstrates separate rod and cone contributions, but which in Oguchi's disease demonstrated an absence of the longer latency rod component. Following prolonged (24 hours) adaptation, at a period when the dark adapted thresholds were normal, the ERG still showed only a small rod contribution with the waveform still being negative.

This abnormality of the rod system even after prolonged adaptation was further emphasized by the computer averaging technique (Figure 10B). By this technique very low intensity stimuli were used which did not affect the subject's normal dark adapted level. While Carr and Ripps[45] had demonstrated that a very weak white light stimulus will elevate the visual threshold for a prolonged period of time, the use of a low intensity red light did not affect the threshold. In the normal, following dark adaptation, summed responses showed a well-delineated double wave. By contrast the patient with Oguchi's disease showed a normal initial cone response while the rod response was very reduced in size and had a latency delay of 40 msec.

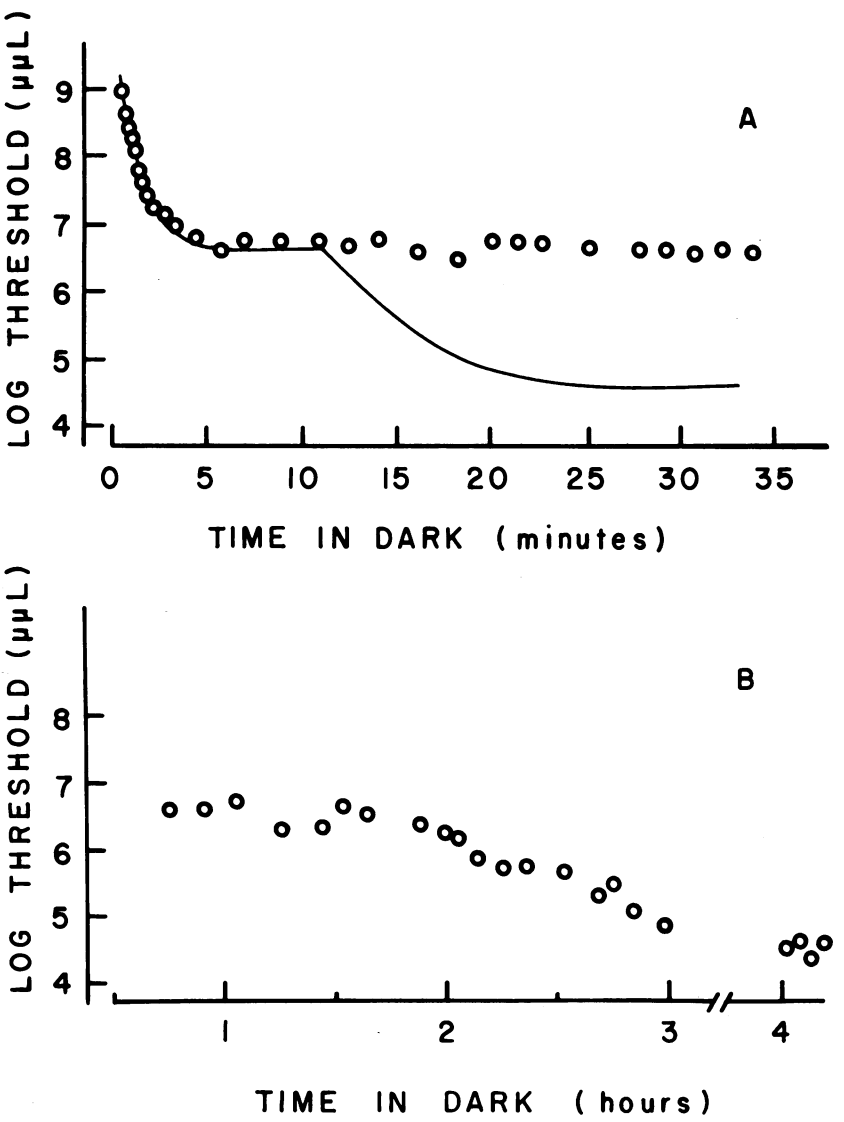


FIGURE 9

Oguchi's disease. Course of dark adaptation following 7 minutes' exposure to a luminance of 8900 cd per square meter. Data are for a 4.5 degree test field located 12 degrees nasal to fixation. The continuous curve represents the normal function for equivalent test conditions. Note the change of time base between the upper and lower segments of the figure.

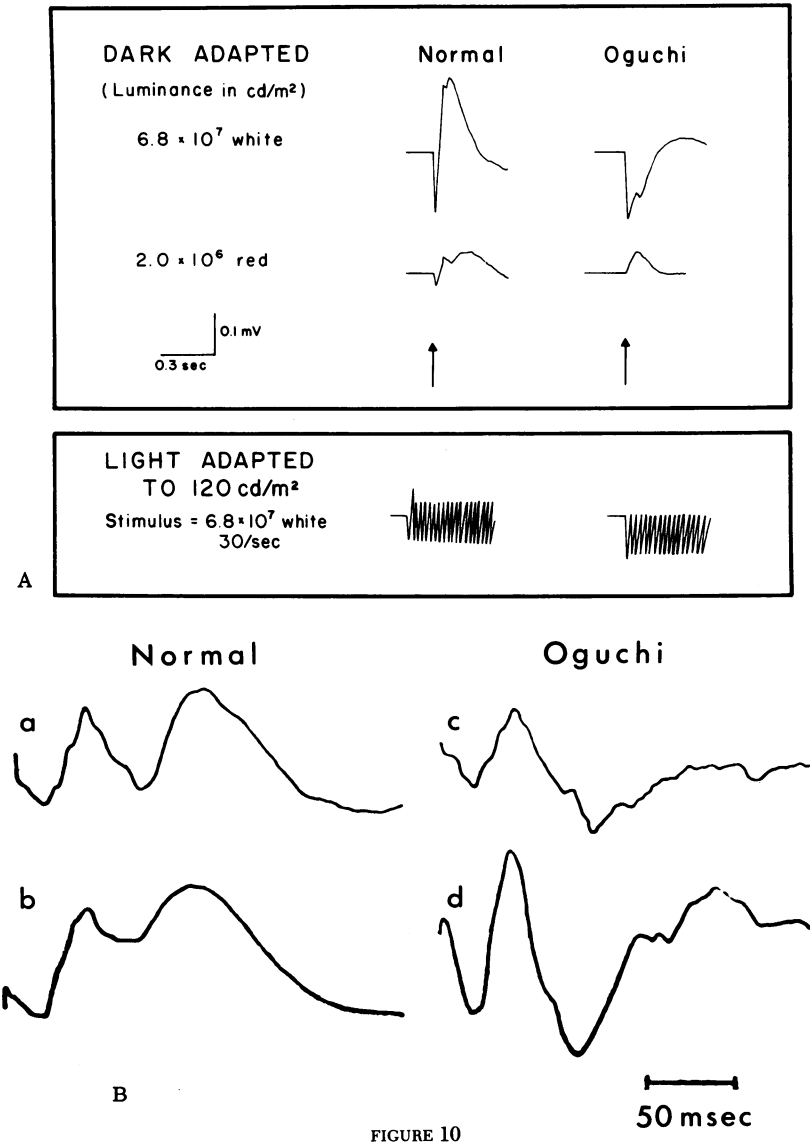


FIGURE 10

A. Oguchi's disease. Electrical responses elicited under both dark adapted and light adapted conditions. In the dark adapted state both a maximum intensity white flash as well as a maximum intensity red flash were utilized. B. Oguchi's disease. Computer summated electroretinographic responses to 200 flashes of red light at two separate intensities. Segments a and c show responses to a flash luminance of 1.25×10^5 cd/m² and segments b and d show responses to a flash luminance of 2.0×10^6 cd/m². Segment b was recorded at 0.5 log units less gain than the other responses.

Electrooculography (Figure 11A) demonstrated a normal light peak/dark trough ratio of 205% in the right eye and 209% in the left eye, figures well above the lower limit of normal (180%).

The density difference spectrum measurements (Figure 11B), performed in the same peripheral retinal region as used for dark adaptometry, was normal in shape and magnitude and rhodopsin regeneration (Figure 12A) was identical to that of the normal. Thus, all measures of the visual pigment were clearly within normal limits.

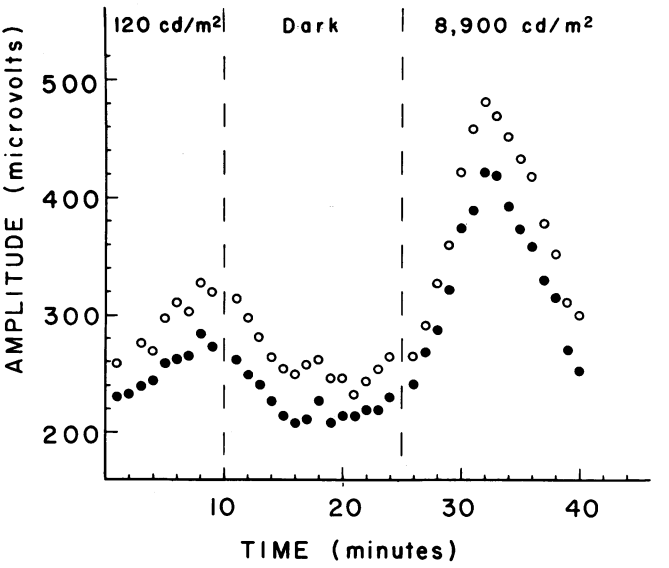
ABNORMAL FUNDI: FUNDUS ALBIPUNCTATUS

Dark adaptometry (Figure 12B) demonstrated a marked delay in both cone and rod function. In the normal, illustrated by the dashed line, there was a rapid descent to the cone level with threshold being attained in approximately 12 minutes. Rod function then became evident and the normal final threshold was reached in approximately 30 minutes. In fundus albipunctatus, a similar pre-adaptation light led to an initial rapid fall in threshold but the rate of descent slowed markedly so that a normal level was reached only after 60 minutes. There was no evidence of a rod-cone break until 140 minutes at which time there was an abrupt transition to the second (rod) branch of the curve. There was again a slow fall until the final dark adapted threshold was reached after 3 hours of adaptation. In spite of thes slow rates of adaptation the final thresholds of both rods and cones are at the same level as the normal.

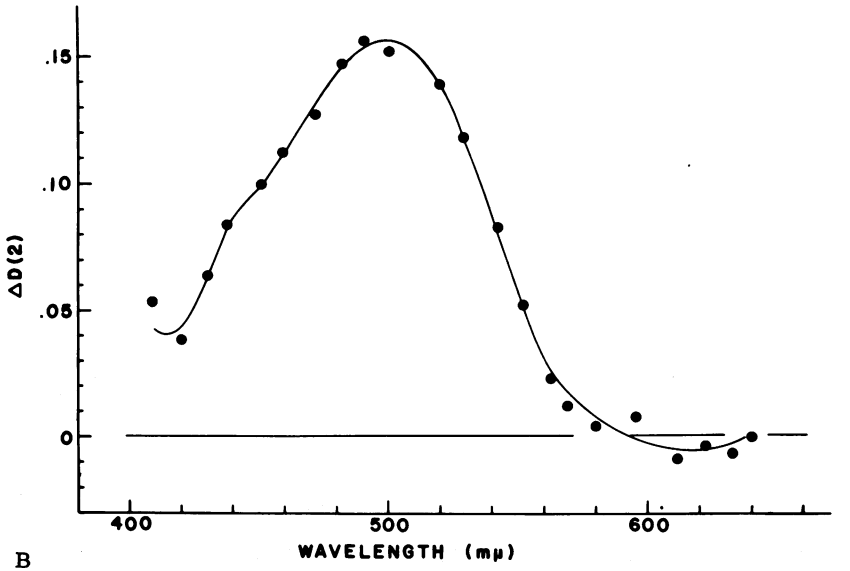
The time at which the cone-rod transition occurred deserves mention. Since rod thresholds are masked by the greater sensitivity of the cone mechanism during the initial 140 minutes of adaptation, the form of the rod curve cannot be easily established. However, if it is assumed that the curve describing rod function decays exponentially, then extrapolating back in time indicates an indeterminate level (e.g. > 20 log units above absolute threshold).

FIGURE 11 *(opposite)*

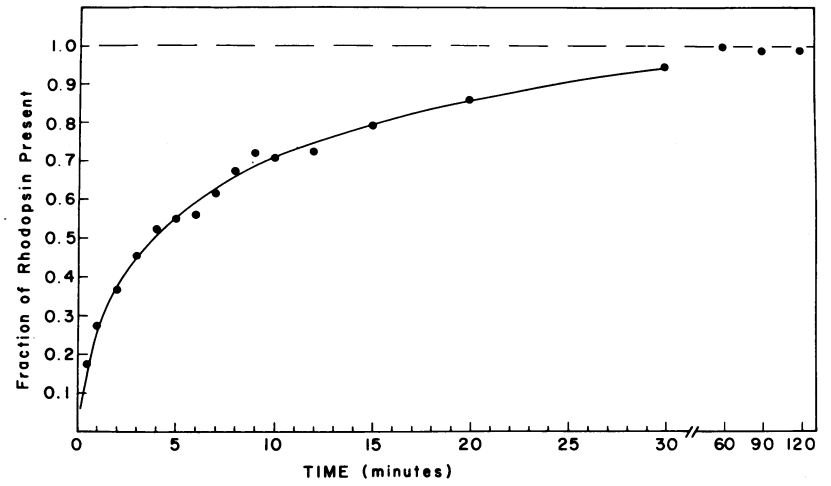
A. Oguchi's disease. Electrooculograms recorded at three levels of retinal illumination for the right (filled circles) and left (open circles) eyes of a subject. Each point represents the average of five pen swings in microvolts. The rise in potential at the highest luminance level is given as a ratio of the light peak to the dark trough. For this subject the values were 205% OD and 209% OS, both above the lowest limit of normal (180%). B. Oguchi's disease. Difference spectra measured at 12 degrees in the temporal retina. A white bleaching light of 7.5 log troland seconds was used. The ordinate $\Delta D(2)$ gives the density change for double transit through the retina; density losses due to bleaching are plotted as positive values. A best fit line is fitted to the data point.


120 cd/m²
Dark
8,900 cd/m²
AMPLITUDE (microvolts)
500
400
300
200
10
20
30
40
TIME (minutes)

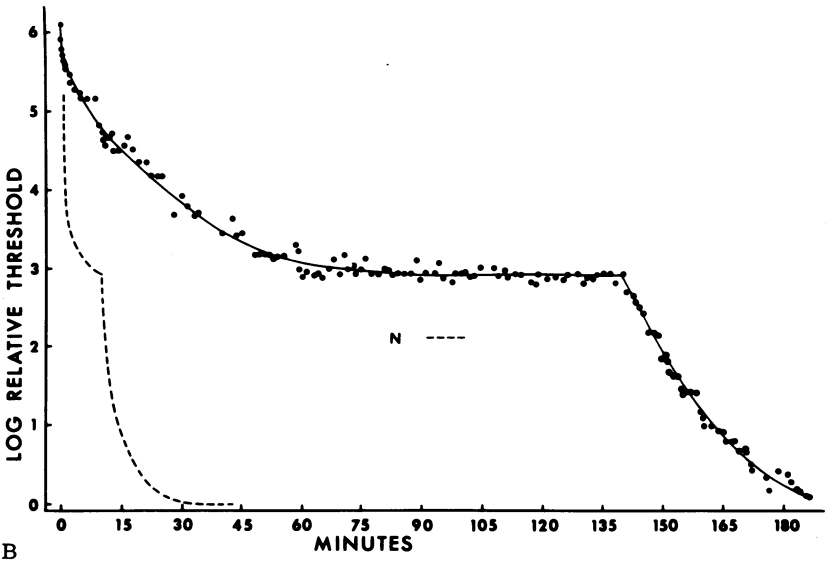
A


.15
.10
.05
0
ΔD(2)
400
500
600
WAVELENGTH (mμ)

B



A



B

FIGURE 12

A. Oguchi's disease. Rhodopsin regeneration. Results were obtained from density difference measurements (λ = 500 nm) taken during the course of dark adaptation. The initial exposure was 7.5 log troland seconds. The ordinate scale gives the rhodopsin density relative to the value obtained after 4 hours dark adaptation (dashed line at f = 1). B. Fundus albipunctatus. Course of dark adaptation following 7 minutes' exposure to a luminance of 8900 cd per square meter. Data are for a 4.5 degree test field located 12 degrees nasal to fixation. The dashed line represents the normal function for equivalent test conditions.

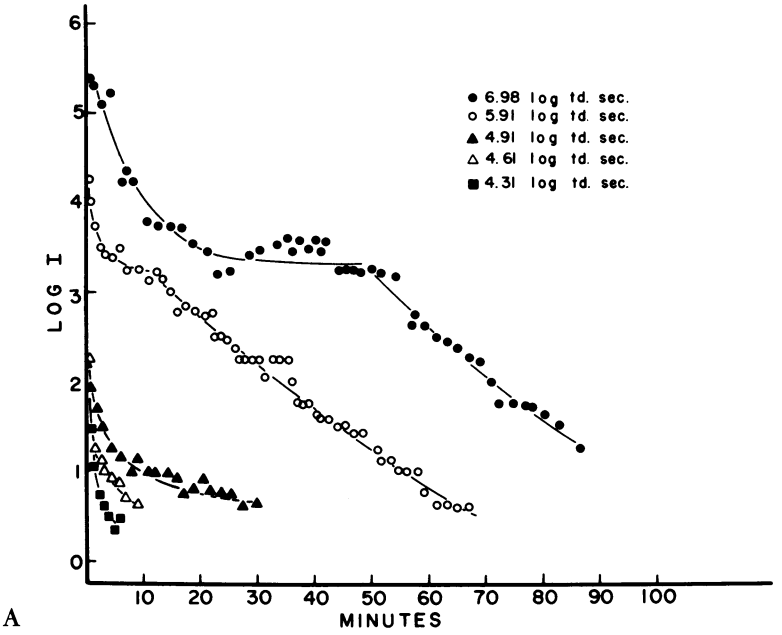
Various bleach intensities were utilized to study rates of adaptation (Figure 13A), and the rates of both cone and rod adaptation were clearly dependent on the intensity used. In all cases the bleach was given after the patient was fully dark adapted so that with the three lowest intensity bleaches cone threshold was not even obtained. The bleach of 4.91 log td seconds is of particular interest for it is a value selected to match that previously used by Carr and Ripps[45] in testing a patient with Oguchi's disease. Although this intensity bleaches less than 0.8 per cent of the available rhodopsin, in Oguchi's disease such an exposure elevated rod threshold above the cone level and caused it to remain there for more than 30 minutes of subsequent dark adaptation. In fundus albipunctatus, however, there is a much less of an effect, with thresholds returning rapidly to the dark adapted level. This rate of adaptation is not as rapid as normal, however, where normal thresholds are attained in ten minutes.

Electroretinography (Figure 13B) provided another parameter by which to demonstrate the slow recovery of function after photic exposure. Electrical responses during adaptation to a dim blue light (S_1B) are illustrated. In fundus albipunctatus the scotopic b-wave was essentially absent until 60 minutes of adaptation at which time there was a slow rise until normalcy was attained after 140 minutes. The amplitude change of these waves is noted by the closed circles while the form of the ERG response in fundus albipunctatus is illustrated on top. The normal increase of b-wave amplitude to this low intensity blue stimulus is illustrated by the open circles, with the response reaching maximum by 20-30 minutes.

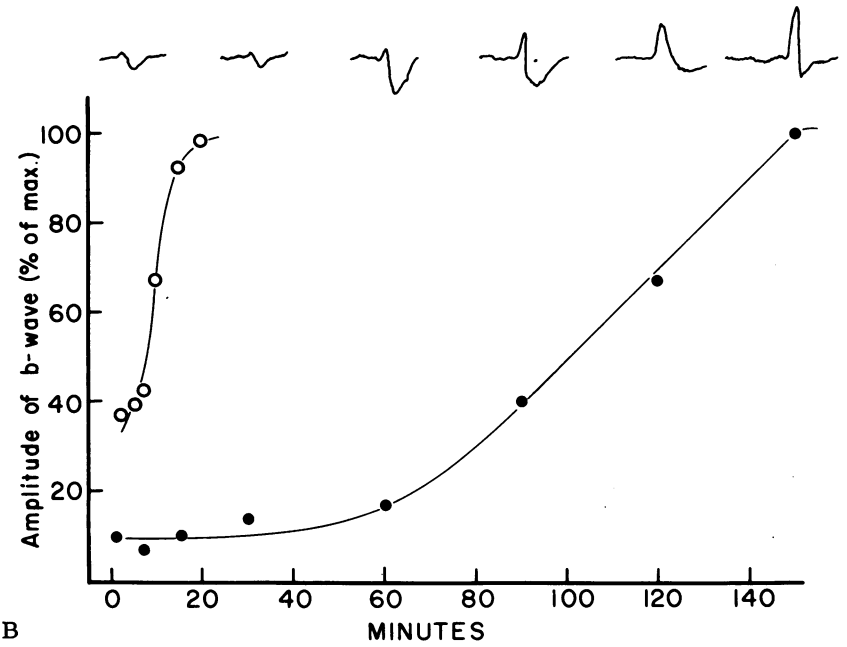
Electrooculography (Figure 14A) showed a clearly abnormal light rise (140%) when this was obtained after the normal dark adapted period of 15 minutes. However, with a prolonged dark adaptation period of 3 hours the EOG light rise reached 235%, a ratio clearly within normal limits.

Density difference spectra as measured in the retinal periphery are illustrated in Figure 14B and compare a patient with fundus albipunctatus (left) to a normal (right). Difference spectra are recorded at various times in darkness following exposure of the test area to a retinal illuminance of 7.5 log td-sec. While in the normal full amplitude of the response is reached in 20 minutes, a time period of 2½ hours was necessary in fundus albipunctatus.

Another important difference between fundus albipunctatus and the normal is in the peak wavelengths (λ_{max}) of the regeneration-difference spectra. While in the normal there is a progressive shift in λ_{max} from 490 nm after 30 seconds to 510 nm after 20 minutes, for the subject with


● 6.98 log td. sec.
○ 5.91 log td. sec.
▲ 4.91 log td. sec.
△ 4.61 log td. sec.
■ 4.31 log td. sec.
LOG I
MINUTES

A


Amplitude of b-wave (% of max.)
MINUTES

B

FIGURE 13 *(opposite)*

A. Fundus albipunctatus. Course of dark adaptation following exposure to the luminances noted. Free hand curves are drawn through the experimental data. B. Fundus albipunctatus. Growth of electroretinographic b-wave amplitude to a dim blue flash following preadaptation to a luminance of 8.02 log troland seconds. A normal subject (open circles) is compared to an affected (closed circles). Some of the actual ERG tracings obtained at selected time intervals are shown above the graphs.

fundus albipunctatus the spectral shift is in the opposite direction, that is from 510 nm at 20 minutes to 500 nm after 150 minutes.

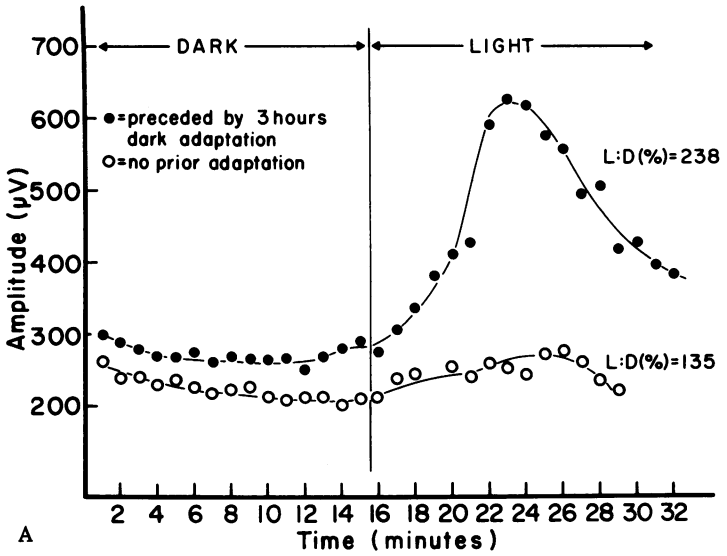
This marked delay was made further evident in considering rhodopsin regeneration (Figure 15A). In the normal, illustrated by the hatched lines, the half-time of rhodopsin regeneration is about 3 minutes[75] while the half-time of regeneration in fundus albipunctatus was markedly delayed, not occurring until 60 minutes in darkness.

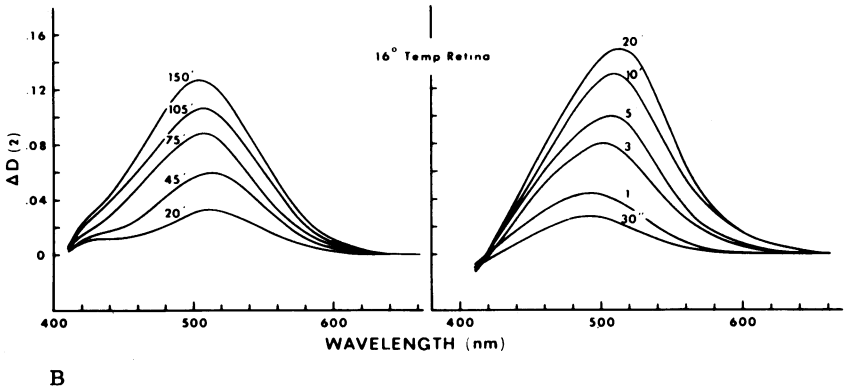
Cone pigment regeneration (Figure 15B) was likewise delayed, a finding in keeping with the prolongation of cone adaptation noted in adaptative measurements. There was good correlation between the fall in cone threshold (closed circles) and regeneration of cone pigments (open circles). A normal dark adaptation curve is illustrated by the hatched line. While normal cone pigments show a half-time of regeneration of 75 seconds,[76] in fundus albipunctatus the half-time is increased to 20 minutes.

DISCUSSION

NORMAL FUNDI

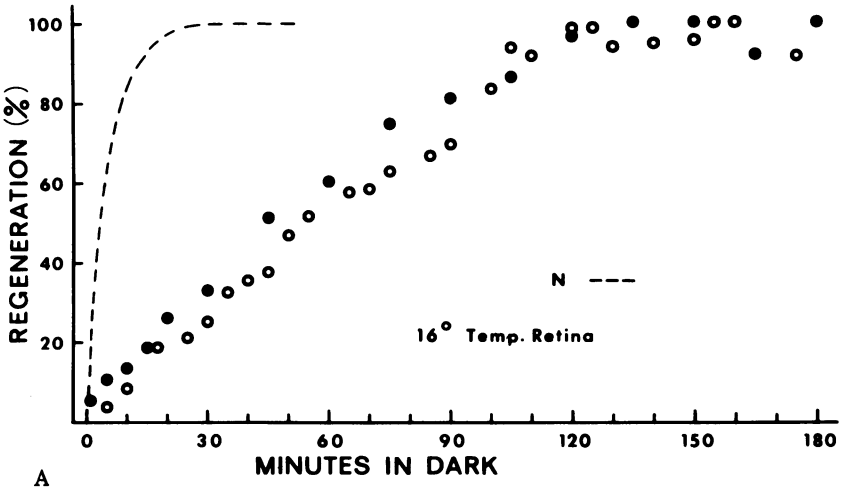
This group logically divides into two major types on the basis of electrophysiologic data. In one the ERG shows a very reduced photopic response, there is no scotopic increment, and the EOG is abnormal. The second variety shows a "negative" ERG in which the negative component appears of normal size under both light and dark adapted conditions, the positive b-wave is markedly reduced or absent, and the EOG is normal. While the former type was originally described in cases with dominant heredity and is, in fact, referred to as the "Nougaret-type" in regard to the ERG responses, Auerbach et al[21] clearly showed that the ERG pattern bears no relationship to heredity. It is of interest, however, that those patients with myopia and nyctalopia all showed a similar type ERG pattern (negative) irrespective of the mode of inheritance, a finding also noted by other authors.[9]



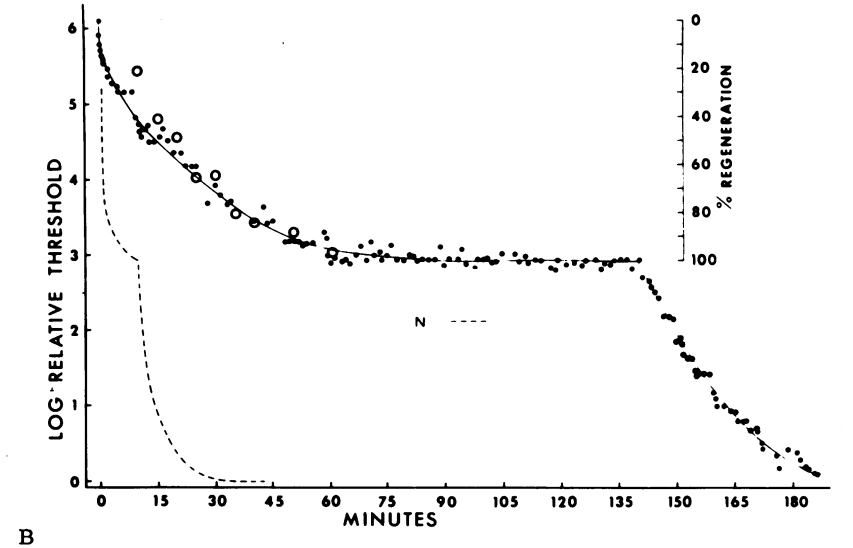


FIGURES 14

A. Fundus albipunctatus. Light-induced changes in the EOG after a 15 minute period in the dark (open circles) and following three hours of adaptation to darkness (closed circles). The light:dark ratio reaches normal levels (i.e. greater than 180%) only after the prolonged stay in darkness. B. Fundus albipunctatus. Density difference spectra measured in the peripheral retina during the course of dark adaptation following exposure to a white bleaching light of 7.5 log troland seconds. A normal (right) is compared to an affected (left) at the times indicated.



A



B

FIGURE 15

A. Fundus albipunctatus. The regeneration of rhodopsin for two different patients. The normal course of rhodopsin regeneration is illustrated by the hatched line. To minimize the influence of absorbing photoproducts 540 nm was selected as the measuring wave-length. B. Fundus albipunctatus. The same dark adaptation curve illustrated in Figure 20 is presented. The open circles represent the regeneration course of cone pigments for an affected subject. To minimize the influence of absorbing photoproducts 590 nm was selected as the measuring wavelength. See text for details.

In both of these forms the results of fundus reflectometry clearly demonstrate that rhodopsin is present in normal concentration, that the regeneration of rhodopsin is normal, and by inference from the amount of rhodopsin, that the number of rods is likewise normal.[77] Thus, if rhodopsin and the photoreceptors are normal in all respects one must look elsewhere for the basic abnormality in this disorder.

In the patients with an overall reduction in the ERG responses (that is Nougaret-type) it is clearly seen that not only is there an absence of the large b-wave response, but the initial a-wave is also attenuated. Evidence has accrued that this latter response derives from the inner segments of the photoreceptors[78,79,80] and it is probably at this site that the lesion producing this form of nightblindness resides. While the possibility of an abnormality in the functioning of the outer segments cannot be completely ruled out, since little is known of the mechanism by which electrical activity is generated following isomerization of visual pigment molecules, it would seem unlikely in view of the normalcy of the visual pigments and the close relationship between the pigment epithelium and outer segments with regard to pigment kinetics.

The abnormality of the photopic system is also evident from the reduced size of the ERG responses, thus confirming previous studies in which this was noted.[17,18,19,20,22,26,32] This electrophysiologic abnormality ties in with the psychophysical finding of a dark adapted final threshold which is above even the normal cone level.

The EOG is also seen to be markedly abnormal, demonstrating no real light rise but instead showing just oscillations around the baseline comparable to that seen in any individual in whom there is no change of illumination. While some authors felt that the light rise of the EOG was generated by the interaction of the pigment epithelium and rod outer segments during Vitamin A exchange,[72] the findings of Carr and Siegel,[25] and Gouras and Carr[81] seem to provide a more likely explanation of the EOG light rise. These authors reported an absence or a marked reduction of the light rise following anoxia of the inner retinal layers and thus concluded that this rise was dervied from an area proximal to the receptors, probably intermediate between those areas responsible for the a- and b-waves of the ERG.

Thus, this particular form of CSNB seems to involve a defect in neural transmission at the level of the receptor inner segments with the precise nature of the defect remaining unknown.

The patients with a "negative" ERG have considerably different electrophysiologic functions, thus suggesting that the defect occurs at a different retinal level than the variety just discussed. In these cases the a-wave

of the ERG as well as the EOG light rise are normal, thus indicating normalcy of the outer retinal layers. The b-wave, however, is grossly abnormal. Since the b-wave originates from the bipolar cell region,[79,82] the absence of any recordable b-wave response would indicate an abnormality in neural transmission in the region of the bipolar cells.

Unlike the other variety of CSNB with normal fundi, the dark adaptation curve is bipartite with a very slight adaptation of the rod system being noted. However, the cone level is likewise above threshold, again evidence that this disorder is diffuse and affects both rod and cone systems.

OGUCHI'S DISEASE

In this disorder, as in the previously described varieties of CSNB, the visual pigments are completely normal with regard to both concentration and regenerative properties. The abnormalities in this form of CSNB again lie in the electrophysiologic tests. While both the a-wave and the EOG light rise are normal, the ERG b-wave is compromised. Thus the region of the bipolar cells appears to be the earliest stage in the visual pathway exhibiting signs of defective function. This locus is similar to one of the varieties of CSNB with normal fundi, but the transient loss of ability to dark adapt suggests that the exact nature of the defect differs in these two conditions.

It is this lack of correspondence between visual sensitivity and the ERG b-wave that is perhaps the most puzzling aspect of this disorder. The electroretinographic defect lies in the absence of the b-wave, a response closely associated with retinal sensitivity.[83,84] Likewise, computer summation techniques with testing being performed at threshold showed only an abortive rod response (Figure 10B). In addition, unlike the previously noted forms of CSNB in which the scotopic system contributes little to vision, patients with Oguchi's disease have a rod mechanism which adapts to a normal absolute threshold while the rate of adaptation is grossly abnormal. This lack of correspondence between dark adaptation and the rate of rhodopsin regeneration implies an altered relationship between these two functions in this disorder. This implication is furthered by the studies of Carr and Ripps[45] in patients with Oguchi's disease. Utilizing a light intensity which bleached only 0.8 per cent of available rhodopsin, they showed an elevation of threshold to the cone level for over 30 minutes. Such a bleach in the normal leads to a return to threshold in 10 minutes.

FUNDUS ALBIPUNCTATUS

In this disorder the defect clearly seems related to an abnormality in visual pigment kinetics. There is essentially a slowing down of pigment regeneration and concurrently a slowing down of all other electrical and psychophysical processes associated with adaptation. Since pigment regeneration is markedly retarded, it follows that all other retinal responses distal to the pigment epithelium and photoreceptor inner segments will likewise be abnormal. However, with full regeneration of the visual pigments all adaptometric parameters also regain normalcy. Thus the abnormality in fundus albipunctatus seems to be a disturbance in the intimate relation between the photoreceptors and the pigment epithelium. It is well-known that the latter is essential for regeneration of visual pigments[85] and serves as a site for the storage and metabolism of Vitamin A.[86] An abnormality in this layer thus might account for the slow rate of regeneration of both the rod and cone pigments. This hypothesis seemingly holds some merit on the basis of the results presented in such patients. In the normal retina the rate-limiting step in the dark adaptation process seems to be the regeneration of bleached visual pigments; both Dowling[87] and Rushton[88,89] have reported a log-linear relationship between visual sensitivity and photopigment concentration. In this view the biphasic curve of subjective adaptation is governed by the recovery rates of the cone and rod photopigments. Indeed, the very marked delay in the appearance of the scotopic segment of dark adaptation suggests a prolonged "silent period", a time during which rods are completely suppressed.[90,91] While it cannot be stated with certainty that a parallel relationship between dark adaptation and rhodopsin regeneration applies in these subjects, since the two sets of data were obtained following different light-adapting conditions, the very similar slowing of all processes makes this hypothesis a likely one.

As an ancillary hypothesis the receptors may not be able to effectively transport their photoproducts or utilize the vitamin A stores of normally functioning pigment epithelial cells. It may be that the prolonged period over which rod and cone thesholds remain elevated is due to the presence of the products of bleaching which in fundus albipunctatus may decay slowly. Examination of the density difference spectra (Figure 14B) over the course of dark adaptation show a marked difference between the λ_{max} of the normal and the patient with fundus albipunctatus. Ripps and Weale[75] have shown in the normal that the displacement of the λ_{max} from 490 nm to 510 nm during the course of pigment regeneration is due to the formation and subsequent decay of an intermediate product of bleaching, presumably metarhodopsin III. If such a photoproduct were to be present for an unusually long time period, not only would delay in pigment regeneration

result, but λ_{max} would be expected to shift to longer wavelengths with photoproduct accumulation. The studies of Ernst and Kemp[92] further strengthen such an argument. These authors have shown that prolonged retention of an intermediate photoproduct of bleaching exerts a profound effect on the responses of the photoreceptors such that certain ERG responses show a linear dependence on the concentration of the final products of rhodopsin decomposition. Thus, the slow evolution of the ERG responses (Figure 13B) would be in keeping with such a theory.

While all questions are not resolved in these various disorders of CSNB, such conditions provide a unique opportunity to study the relationships between photochemical events, electrical responses, and visual sensitivity.

SUMMARY

The various forms of congenital stationary nightblindness (CSNB) are presented and can be divided into those with normal fundi and those in which the fundus is abnormal. On the basis of electrophysiologic and psychophysical tests, as well as a study of the visual pigments *in vivo*, the basic abnormality in these disorders can be suggested. In the disorders with normal fundi as well as Oguchi's disease, visual pigments are normal, both in amount and kinetics, and the basic abnormality seems one of neural transmission at certain levels of the outer retina. In fundus albipunctatus, visual pigment kinetics and electrophysiologic tests of retinal function are greatly retarded and the basic defect in this disorder seems one of retardation in the formation of the visual pigments.

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