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FUNDUS ALBIPUNCTATUS: A CLINICAL STUDY OF THE FUNDUS LESIONS, THE PHYSIOLOGIC DEFICIT, AND THE VITAMIN A METABOLISM

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ABSTRACT

Two unrelated patients with fundus albipunctatus, each the product of a consanguinous marriage, were studied with reference to their fundus lesions, their physiologic deficit and their vitamin A metabolism.

Both patients showed albipunctate lesions that appeared deep to vessels and either blocked fluorescein or were invisible on angiography. Some of the lesions changed during a 1-2 year observation period. In one patient the lesions showed a radial arrangement in the fundus. Both patients showed greatly retarded dark adaptation, measured subjectively or with the electroretinogram. Cone as well as rod dysfunction was involved, and subtle abnormalities of the visual fields and of color vision were found. The a- and b-waves of the electroretinogram were both affected by the disease, suggesting an adaptation defect prior to generation of the a-wave. These findings are consistent with the observation of Carr, Ripps & Siegel (1974) that photopigment regeneration is retarded in this disease. Both patients showed normal blood levels of vitamin A, carotene, retinol binding protein, amino acids, proteins and lipoproteins. The administration of therapeutic levels of vitamin A parenterally and orally had no effect on the rate of dark adaptation or the fundus lesions.

This study supports the view that fundus albipunctatus is a stationary recessive disorder which can be defined physiologically by a slow rate of dark adaptation and visual pigment regeneration, and which is clinically separable from progressive dystrophies such as retinitis punctata albescens. The significance of the albipunctate fundus lesions remains unclear. If vitamin A metabolism is involved in fundus albipunctatus, the involvement must be at a local level.

INTRODUCTION

Fundus albipunctatus is a rare form of stationary 'night blindness' in which a myriad of white dots are visible in the fundus. Lauber (1910) distinguished it from retinitis punctata albescens which can have a similar fundus appearance but is a severe progressive dystrophy. Some authors feel these disorders form a continuum (Franceschetti et al., 1974) while others (Carr, 1974; Marmor, 1977) feel they are separate entities. Carr et al. (1974) studied two brothers with fundus albipunctatus and showed by fundus reflectometry that dark adaptation was extremely slow and corresponded to an abnormal rate of visual pigment regeneration. These findings suggest a possible relationship of fundus albipunctatus to vitamin A metabolism; furthermore,

albipunctate fundus lesions may be seen in vitamin A deficiency (Uyemura, 1928; Teng, 1965) and abetalipoproteinemia (Gouras et al., 1971).

The present study provides detailed clinical information about two families with fundus albipunctatus. The fundus lesions have been analyzed with fluorescein angiography and serial photography in an effort to determine their location and constancy. Physiologic testing was performed using both subjective and electrophysiologic techniques, to help document the site of the dark adaptation defect and the degree of cone involvement. The blood levels of vitamin A and retinol binding protein (as well as other substances such as amino acids and lipoproteins) were measured, and a trial of vitamin A therapy instituted, to determine whether systemic vitamin A has any role in this disorder.

METHODS

Dark adaptometry

Performed on an automated Goldmann-Weekers adaptometer (Gunkel & Bornschein, 1957) using an 11° test field, 11° below a red fixation target and 30 cm from the eyes. The pupils were dilated and the patients were preadapted for 7 minutes to an intensity of 425 footlamberts. Exposure to the test light during adaptometry has minimal effect on the adaptation time of normal subjects (Gunkel & Bornschein, 1957). To control for such an effect during the prolonged testing of these patients, one eye was covered after binocular pre-adaptation to light. At infrequent intervals, the covered eye was unpatched to compare its threshold and confirm that there was no significant difference between the eyes.

Electroretinograms (ERG's)

Flashes were produced by a Grass PS-2 photostimulator whose lamp rested on top of a full-field stimulator (Marmor, 1976). The signals were recorded differentially with bipolar Burian-Allen electrodes, using high-gain oscilloscope amplifiers (Tektronix 5A22), and a storage oscilloscope (Tektronix 5103). The pupils were dilated for all ERG's. Cone responses were produced by a bright white flash (W-8) against a 15 foot-lambert background or at a rate of 25-3 Hz. Rod responses were produced after 15 minutes dark adaptation (in a normal subject) by a flash nearly 2 log units weaker (W-1 + 1-ND). A W-8 flash after dark adaptation produced a large amplitude ERG with mixed cone and rod components. At least two stimuli were presented and photographed under each condition (10-15 seconds apart) to insure that the waveforms were reproducible.

Dark adaptation of the ERG components

One eye was patched at the beginning of dark adaptation, and at selected intervals the patch was shifted and an ERG lens inserted into the newly uncovered eye under dim red illumination. Bright stimulus flashes were kept to a minimum (never more than four, 15 seconds apart), and these few do not alter the normal ERG and probably do not bleach a significant amount of rhodopsin (Gouras, 1970). B-wave thresholds were determined by the density of filters under the flashlamp which allowed a criterion response of 10 μV.

Chemical analyses

Vitamin A and carotene levels were obtained through Bioscience Labs, Los Angeles, California (modified Sobel-Snow method) and Biochemical Procedures, Inc., San Francisco, California (Bessey method). Retinol binding protein was measured by an immunodiffusion plate (M-Partigen Accupak Kit, Behring Diagnostics). Other blood studies were performed by the clinical laboratories at the Stanford University Medical Center.

Vitamin A administration

Both patients were given therapeutic levels of parenteral or oral vitamin A during two separate trial periods. Aquasol A (water-miscible vitamin A, USV Pharmaceutical) was used for intramuscular injection. For oral supplementation, Case A-3 took a natural oil capsule (Life Laboratories) while Case B-5 took a vitamin A palmitate preparation (McKesson Laboratories). Case A-3 was initially given 100,000 i.u. IM and this was repeated after 48 hours; he then took 50,000 i.u. per day orally for 30 days. After $3\frac{1}{2}$ months without supplement, he took 100,000 i.u. per day orally for 46 days. Case B-5 was initially given a single injection of 50,000 i.u. IM, followed by 25,000 i.u. orally every other day for 20 days and daily for 7 days. After two months without supplement she took 50,000 i.u. per day orally for 55 days. Her father was given one injection of 100,000 i.u. IM.

CASE REPORTS

Family A (see Figure 1A)

Originated in Lumba, on the island of Flores, in the Azores. Only the propositus (Case A-3) is known to be affected. His parents are consanguinous.

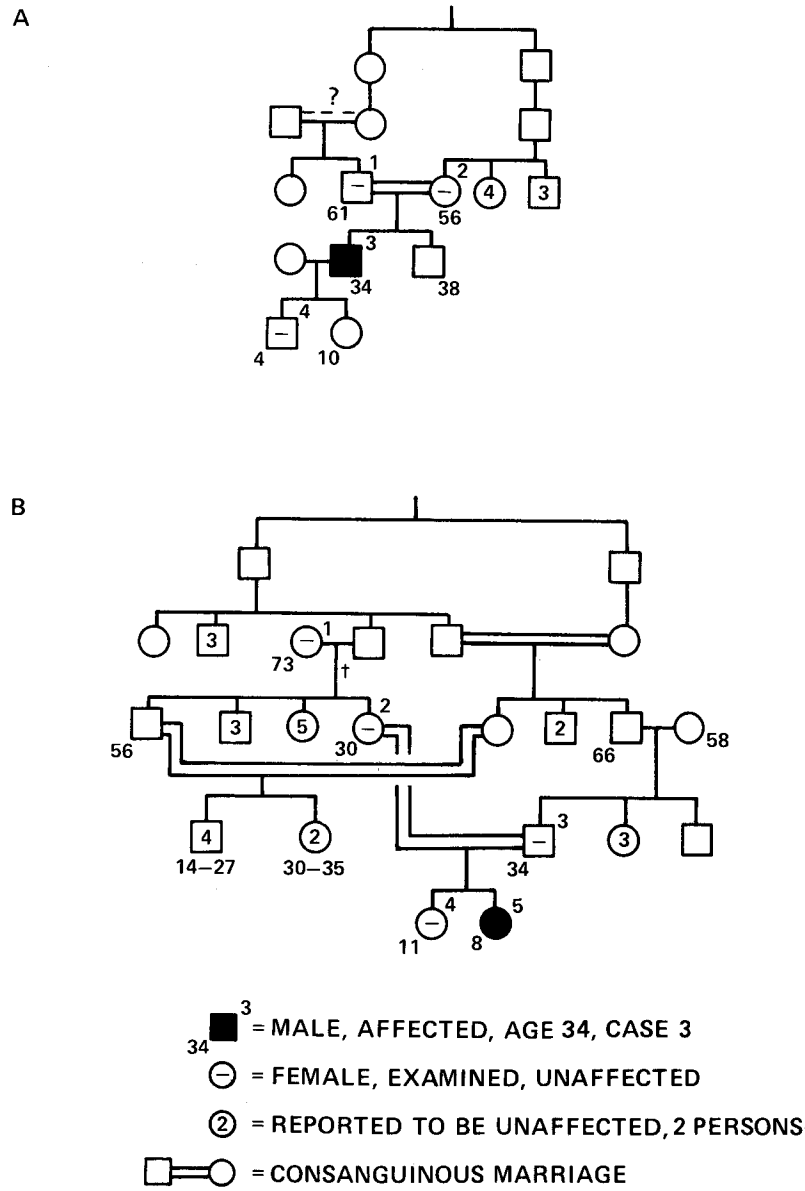

Fig. 1. Pedigrees for Family A and Family B.

Case A-3 (Propositus: male, age 33): His major symptom, which has been stable for as long as he can remember, is slow dark adaptation on going from a bright to a dim environment. At movies, he will finally adapt near the end of a double feature. Past medical and ocular history were unremarkable, and he has taken no significant drugs. Corrected acuity was 20/20 in either eye with a refractive error of −1.50 sph. in OD and −2.00 sph. +1.00 cyl. x 70° in OS. Intraocular pressure was 20 mm Hg OU, and examination of the anterior segment was normal. His fundus appearance is described in the Results.

Case A-1 (father, age 61): No relevant complaints. Corrected acuity was 20/30 in either eye, but the pupils were sluggish, the discs were cupped and he was discovered to have long-standing open-angle glaucoma. The fundus showed some scattered tiny white spots in the posterior pole which are probably small drusen but may conceivably relate to the son's dystrophy.

Case A-2 (mother, age 56): No visual complaints. Corrected acuity was 20/20 on the right and 20/25 on the left. The fundus showed a few tiny white lesions in the posterior pole which may be small drusen or relate to the son's dystrophy.

Case A-4 (son, age 4): No visual complaints. Uncorrected acuity was 20/20 in either eye. The posterior pole appeared entirely normal and without dots. The fundus periphery was rather albinotic with some fine granular pigmentation but this appearance seemed consistent with his age.

Family B (see Figure 1B)

Originated in Seminara in southern Italy. Only the propositus (Case B-5) is known to be affected. Her parents are consanguinous by two possible routes from a common progenitor. Several cousins are also products of a marriage consanguinous by the same progenitor, but are asymptomatic.

Case B-5 (Propositus: female, age 8): Asymptomatic until two years ago when she complained of poor vision on coming indoors from the sunlight. There has been no change in her symptoms over two years. She had measles and ordinary childhood illnesses, but no other medical or perinatal problems. Corrected acuity was 20/20 in either eye with a refractive error in each eye of roughly +1.25 sph. +0.75 cyl. x 90°. The anterior segment was normal. Her fundus appearance is described in the Results.

Case B-1 (maternal grandmother, age 72): No visual symptoms. Vision was

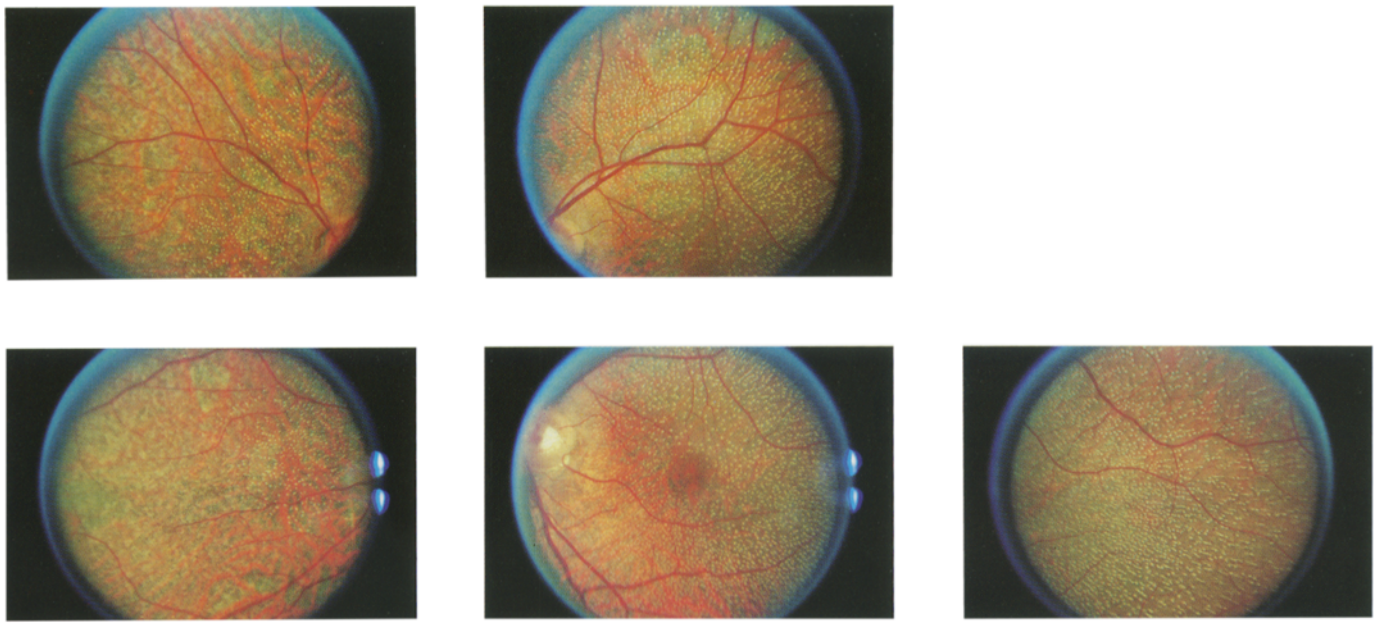

Fig. 2. Fundus photographs of Case A-3. Note the radiating pattern of albipunctate lesions.

20/25 in either eye. The fundi showed arteries attenuated by arteriosclerosis, and extensive large drusen in the posterior pole. There were no discrete white dots or flecks.

Case B-2 (father, age 34); Case B-3 (mother, age 30): Neither had visual complaints, and their acuity was 20/20 in either eye. Their fundi were normal and neither showed any punctate lesions such as noted in the parents of Case A-2.

Case B-4 (sister, age 11): No visual symptoms. Uncorrected acuity was 20/20 in either eye. The fundi showed some granularity and mottling in the equatorial region that seemed within normal limits. There were no discrete white dots or flecks.

RESULTS

Fundus lesions

Figures 2 and 3 show photographs of the fundi of Cases A-3 and B-5, respectively. Both patients showed a scattering of yellow-white dots in the posterior pole, sparing the fovea. Enlarged photographs (Figure 4) show that these dots were sharply demarcated, did not have pigmented borders, and appeared to be deep to retinal vessels. The far periphery showed some diffuse depigmentation, especially in Case B-5, but there were no degenerative pigmentary lesions. The foveas appeared normal in Case B-5 but were dull, lacked a good light reflex, and showed some underlying dispersion of pigment in Case A-3. Both patients had normal optic discs and retinal vessels.

The pattern of fundus lesions is noteworthy. In Case A-3 (see Figure 2), the dots formed rows that radiated out from the macula in a manner which did not correspond to any of the visible retinal or choroidal vasculature. In contrast, the lesions in Case B-5 did not show a radiating pattern. The lesions of both patients showed a striking change in character beyond the vascular arcade, becoming larger and more diffuse to give a mottled appearance to the fundus. These fleck-like peripheral spots were most pronounced in Case B-5 (see Figure 3).

To determine whether the albipunctate lesions were constant or labile, the fundi of both patients were examined serially over time, as well as after vitamin A administration and after dark adaptation. Fundus photographs were taken at intervals spanning a one-year period for Case A-3 and a two-year period for Case B-5. Enlargements of these photographs from both patients (Figure 4) show that some of the lesions definitely changed with time, although a majority were stable. The lability was most prominent in

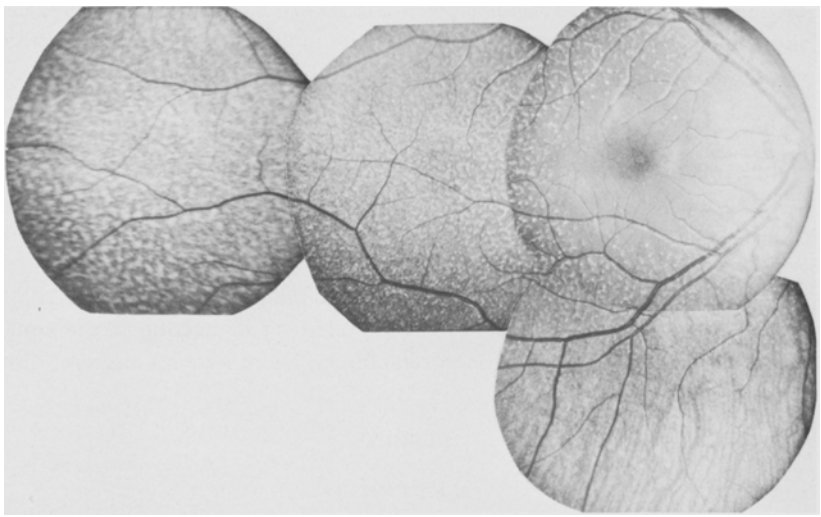

Fig. 3. Composite fundus photograph of Case B-5. By comparison with Case A-3 there are fewer dots, no pattern of radiation, and many fleck-like lesions.

Case B-5 in whom a number of lesions appeared, disappeared or fluctuated at the same site during the period of observation. The 1976 photographs in Figure 4 were taken after one to two months of oral vitamin A administration (see below) which apparently had no effect upon the fundus lesions.

The fundi of both patients were examined by ophthalmoscopy immediately after 3½-4 hours dark adaptation (sufficient to produce a normal rod threshold, but before ambient lighting was restored). A good view was obtained within 1-2 seconds of lighting the fundi, but no change could be discerned in the appearance of the lesions.

Fluorescein angiograms of both affected cases showed normal vasculature and filling times (see Figure 5). There was mottled transmission of fluorescence in both the posterior pole and periphery, but this did not correlate with either the albipunctate lesions or the more peripheral flecks. Angiograms were examined carefully by projection, and photographic enlargement (Figure 6) to study the nature of the fundus lesions. They did not show autofluorescence, and they did not transmit fluorescence. Most of the dots and flecks could not be localized in the angiograms, and those dots that were visible appeared to block fluorescence (arrows in Figure 6).

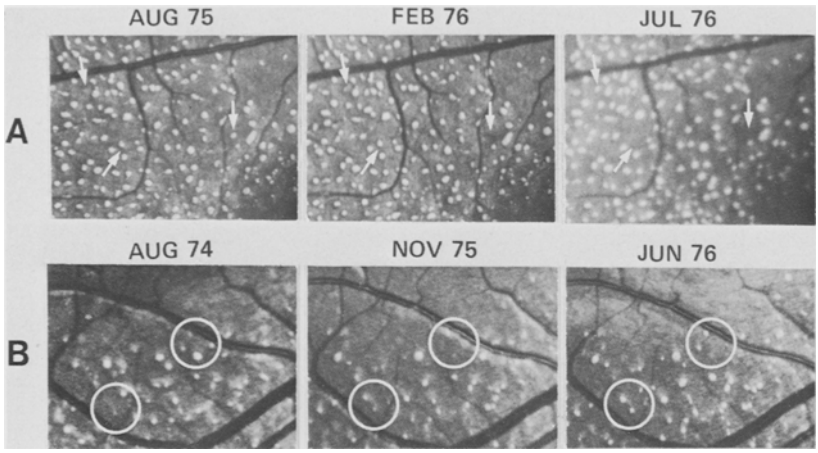

Fig. 4. Enlargements of fundus photographs to show changes in the lesions over time. Vitamin A administration preceded the 1976 photographs. (A) Case A-3. Only a few lesions showed any change (arrows). (B) Case B-5. The lesions showed greate lability, and several within each circle appeared or disappeared over a two-year-period. A few lesions fluctuated in intensity.

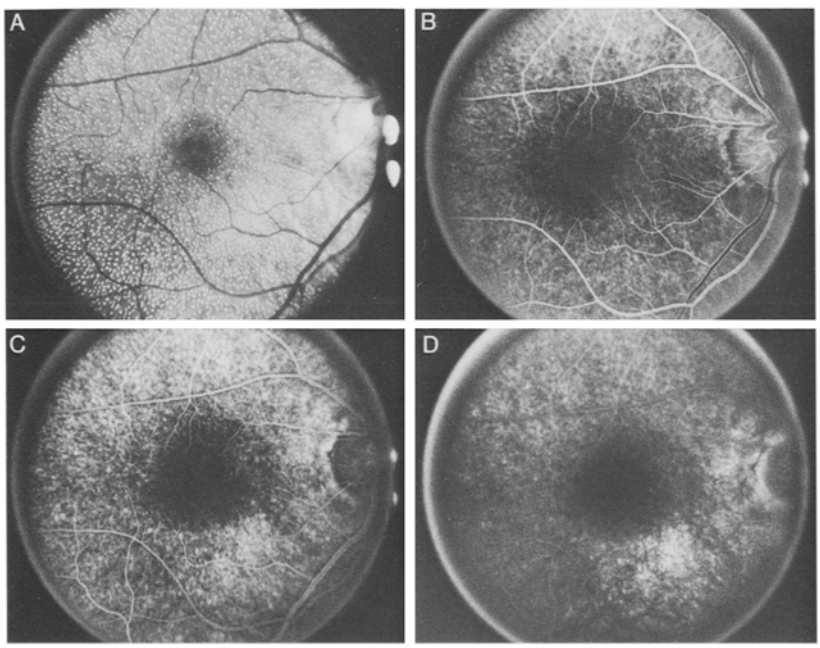

Fig. 5. Fluorescein angiography of the posterior pole in Case A-3. (A) Fundus photograph. (B) Early venous phase (25 sec). (C) Late venous phase (53 sec). (D) Residual fluorescence (10 min). The punctate dots are not easily identifiable in the angiograms (see Fig. 6), and the mottled background fluorescence suggests damage to the pigment epithelium.

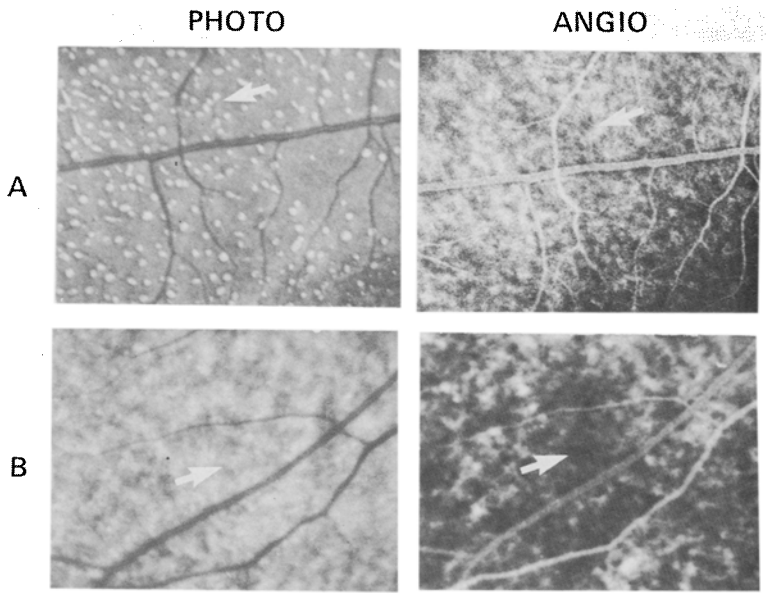

Fig. 6. Comparison of fundus photographs (left) and fluorescein angiograms (right) from Case A-3. (A) Posterior pole; venous phase angiogram (53 sec). Some of the punctate dots appear to block fluorescence (arrow points to a row of four) but many cannot be correlated with the angiogram. (B) Periphery; late angiogram (6 min). There is patchy fluorescence but most of the flecks (e.g. arrow) do not show.

Physiologic data

The visual fields (Figure 7) of both affected cases were normal using a small bright object (I_4) on the Goldmann perimeter, but showed possible constriction (especially Case A-3) to a dimmer target (I_2). Case A-3 had a small paracentral scotoma in either eye, but no equatorial or ring scotoma.

Color vision testing with the Farnsworth D-15 panel on several occasions showed that both patients repeatedly confused one or more adjacent colors. Both cases also had high error scores on the Farnsworth 100-hue test (Case A-3: 201 and 168; Case B-5: 132), and their errors showed a weak tritan pattern (Figure 8). The father of Case A-3 made no errors on either the D-15 panel or the HRR plates. The son of Case A-3 made one error between adjacent colors of the D-15 panel, which is not unusual for a 4-year-old.

The dark adaptation of both affected cases was initially tested in a routine fashion and their 'final thresholds' at 40 minutes were found to be elevated

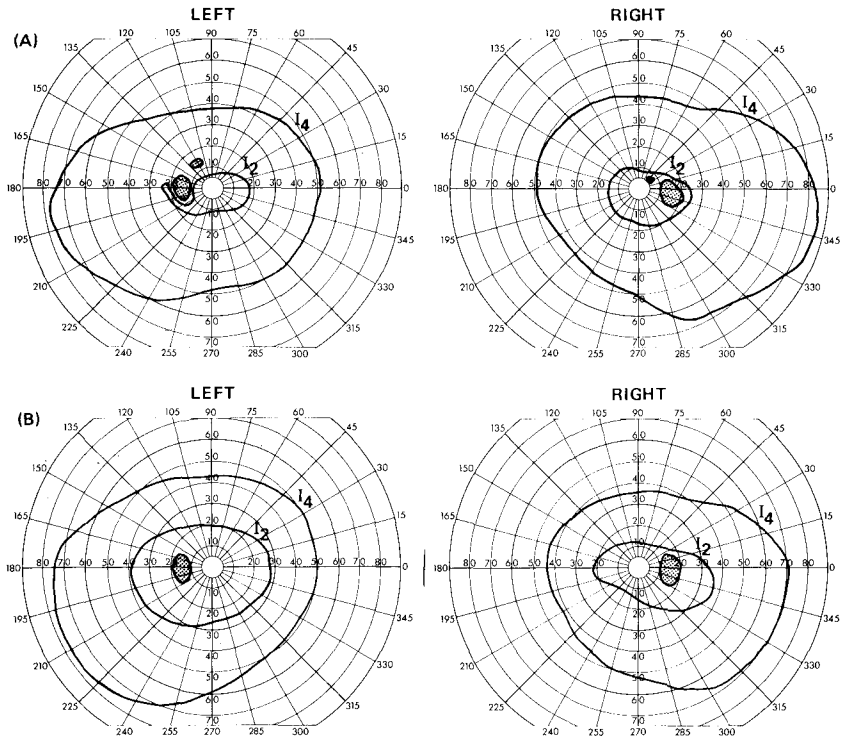

Fig. 7. Goldmann visual fields. (A) Case A-3. (B) Case B-5.

more than 3 log units. (This result from Case B-5 was identical to a record made 15 months previously.) When dark adaptometry was performed for a longer time, both patients showed an extremely slow bipartite curve (Figure 9). The cone plateau was reached at 40-70 minutes, the cone/rod break at 100-120 minutes, and a normal rod threshold at 200-240 minutes. The final configuration resembled a normal dark adaptation curve on a greatly expanded timescale (see Figure 12). The parents of Case A-3 showed normal dark adaptation curves, and a normal final threshold was obtained from Case A-3's 4-year-old son, 30 minutes after pre-adaptation.

Electrooculograms were performed simultaneously on both eyes of Case A-3 after the left eye had been patched for 24 hours and the right eye had about 90 minutes of dark adaptation (Figure 10). Exposure to light produced a large peak (light/dark ratio 2.13) in the fully dark-adapted left eye, but only a minimal peak (light/dark ratio 1.33) in the poorly adapted right eye.

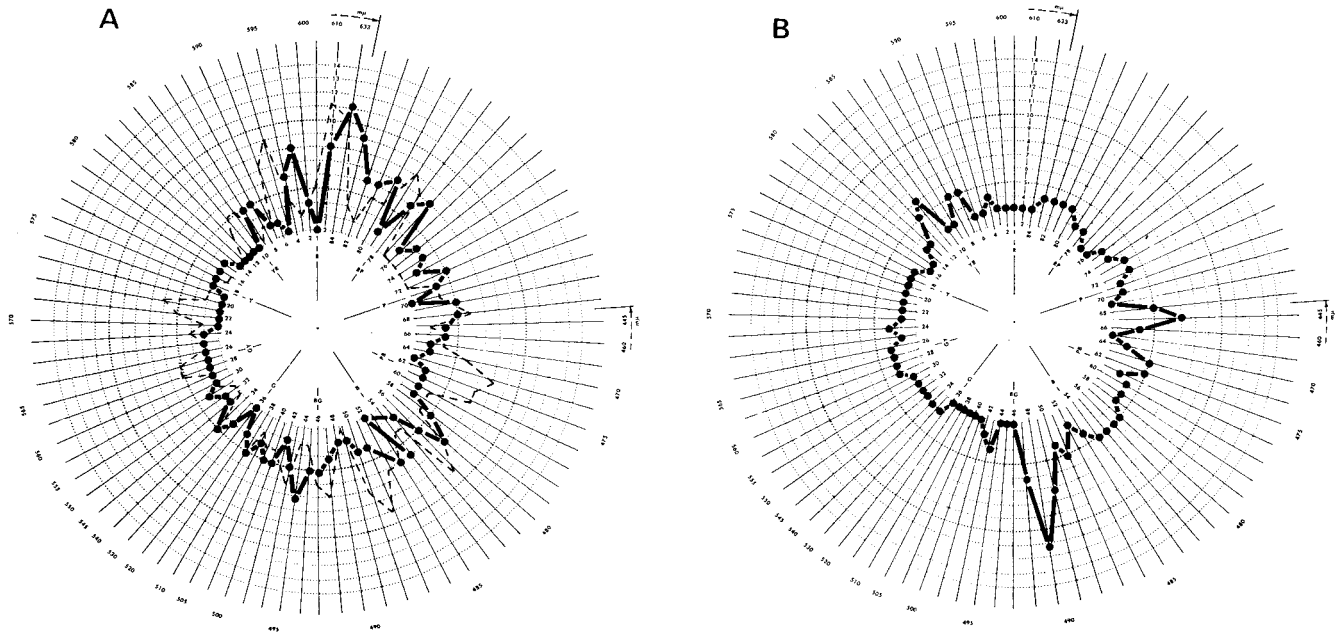

Fig. 8. Farnsworth 100-hue test. (A) Case A-3 on initial testing (dashed line) and retesting (Heavy line). (B) Case B-5.

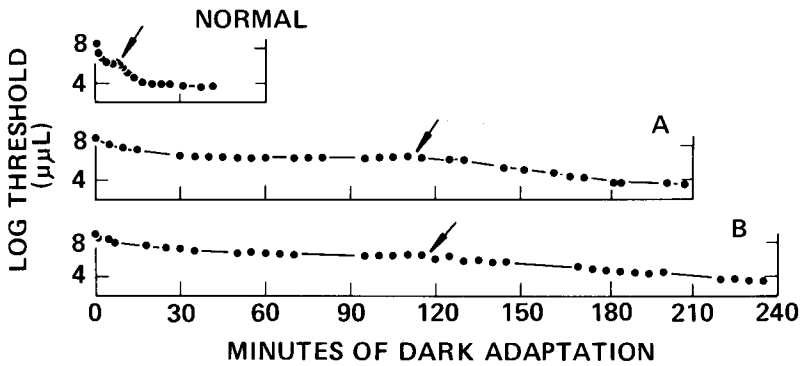

Fig. 9. Dark adaptation curves. (Top) from a normal subject. (A) From Case A-3. (B) From Case B-5. The curves are plotted on an absolute timescale to emphasize the prolonged adaptation time in fundus albipunctatus. Arrows indicate the cone/rod break. These same curves are compared on different timescales in Fig. 12.

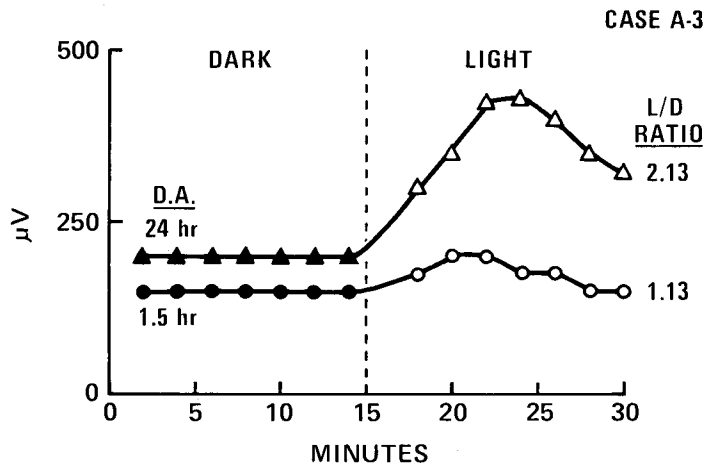

Fig. 10. Electrooculograms from Case A-3. The light/dark ratio was very low (1.33) from the eye which had not been fully dark adapted, but was normal (2.13) from the eye which had been dark adapted overnight.

ERG's were performed on both patients (Figure 11), and the responses were symmetric between the two eyes. The photopic b-waves were of normal amplitude, configuration and implicit time. However, after 15 minutes of dark adaptation, there was no response to a low intensity flash; and a bright flash produced only a cone-dominated signal with a minimal a-wave. (These results from Case B-5 showed no change from records made 15 months

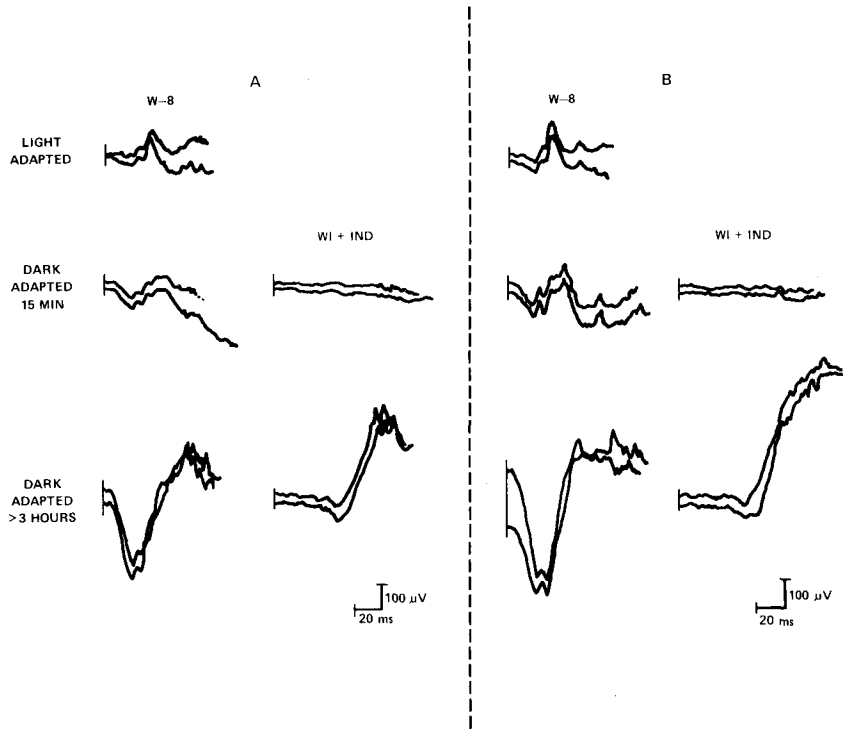

Fig. 11. Electroretinograms. (A) Case A-3. (B) Case B-5. The conditions of light or dark adaptation are shown on the left; the stimulus conditions are shown above each column of responses. W-8 is a bright white flash; W-1 + 1-ND is 2 log units less intense (see Methods). The responses after 3 hours dark adaptation were equivalent to those from a normal individual after 15 minutes.

earlier.) Dark-adapting for $3^1/_2$ hours eliminated these scotopic abnormalities in both patients. A weak flash now produced a 300 μV rod b-wave, and a strong flash produced the typical response of a large a-wave, oscillatory potentials, and a 400 μV b-wave. Note that the stimulus flash was given twice under each condition. This confirms the shape of the waveform and demonstrates that the state of dark adaptation was not altered by a single flash.

The components of the ERG were also studied during the course of dark adaptation to determine whether the subjective and electrophysiologic parameters adapted at the same rate. Data from the affected cases are compared to that from a normal subject (Figure 12). Both the normal and affected individuals showed a strong correlation between the rate of subjective adap-

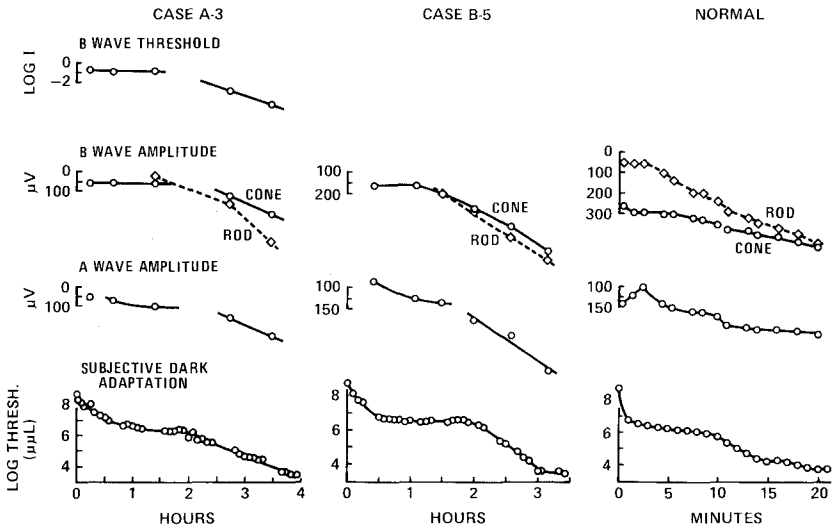

Fig. 12. Subjective and ERG dark adaptation in Case A-3, Case B-5, and a normal subject. Note that the timescale for the two cases reads in hours, but for the normal subject reads in minutes. Subjective dark adaptation curves are on the bottom; ERG components are shown above. Adaptation of the ERG components follows a timecourse similar to that of subjective adaptation in all of the subjects.

tation and changes in the ERG components. The a-wave increased to a plateau during the cone phase of dark adaptation, and then increased further after the cone/rod break. (A brief initial decrease in a-wave amplitude was observed in the normal subject, probably as a result of growth of the cone b-wave.) The cone b-waves remained relatively constant during the cone plateau of dark adaptation, but rose in amplitude (accompanied by the growth of a rod b-wave) during the rod phase of dark adaptation. B-wave thresholds were studied with Case A-3 and showed an initial plateau followed by descent after the cone/rod break.

Blood chemistry and vitamin A administration

Vitamin A and carotene levels for Cases A-3 and B-5, the unaffected parents of Case B-5, and two normal controls are shown graphically in Figure 13. All showed normal values except that the levels of Case B-5 and her parents were borderline low by the Bessey (but not Sobel-Snow) method. The concentration of retinol binding protein was measured immunologically in serum from the same individuals, and was near or above the norm in all of them (Figure 14).

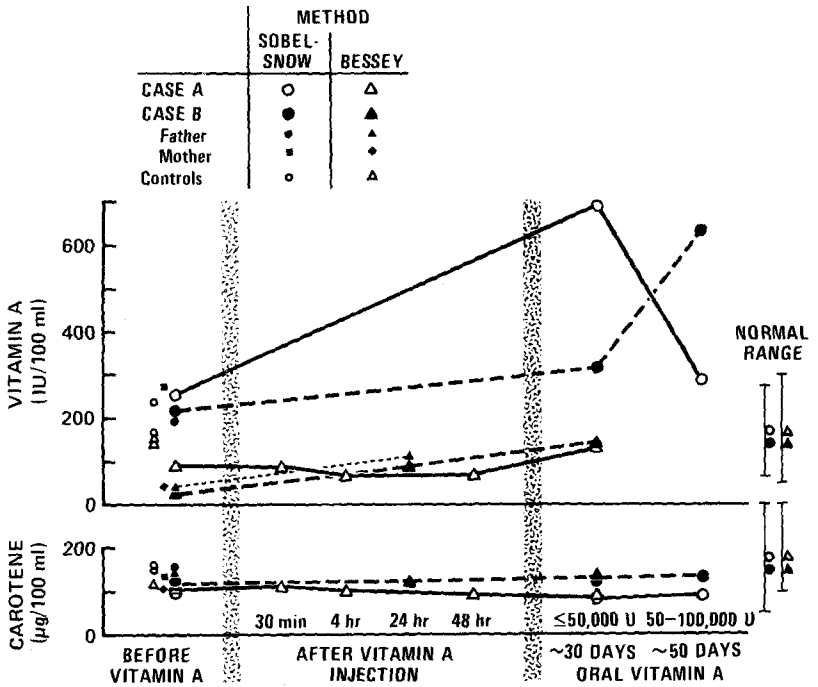

Fig. 13. Serum levels of vitamin A and carotene, before and after vitamin A administration. The serum was independently analyzed by two laboratories using different methods.

Other substances were also studied in the two affected patients. Amino acids* were measured quantitatively in the plasma by ion-exchange chromatography and showed no consistent abnormalities except an absence of measurable citrulline which is not an unusual finding for the laboratory. Both had a normal total amino acid concentration and a normal serum protein electrophoresis. Indirect plasma lipoprotein fractionation showed a low HDL (*a*) cholesterol level in Case A-3, but otherwise normal values in both patients. Organic acids were analyzed in urine from Case A-3 (after he had received vitamin A) and no abnormalities (including phytanic acid) were found.

* phosphoserine, phosphoethanolamine, taurine, hydroxyproline, aspartic acid, threonine, serine, asparagine, glutamine, proline, glutamic acid, citrulline, glycine, alanine, A-amino-N-butyric acid, valine, cystine, methionine, isoleucine, leucine, tyrosine, phenylalanine, B-alanine, baib acid, gaib acid, ethanolamine, allo-delta hydroxylysine, ornithine, 1-methylhistidine, lysine, histidine, 3-methylhistidine, carnosine, arginine.

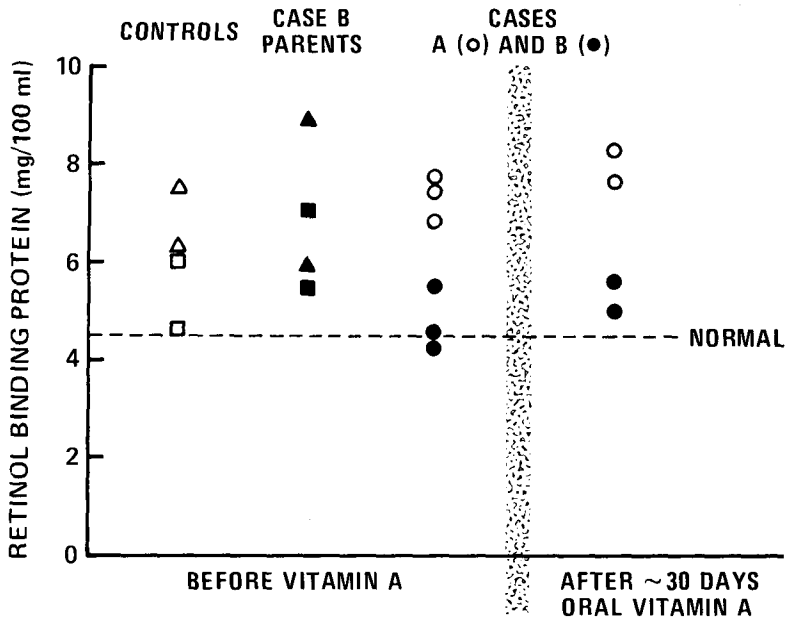

Fig. 14. Serum retinol binding protein before and after vitamin administration. The manufacturer of the test kit described the normal value, but did not indicate a range.

Vitamin A was administered parenterally and orally to both patients as described in the Methods, and its effect on serum levels of vitamin A and carotene are shown in Figure 13. The injections of 50-100,000 i.u. had no effect on Case A-3, but raised the vitamin A levels (Bessey method) of Case B-5 and her father to within the normal range. Oral vitamin A for one to two months caused a rise in serum levels to the mid-range of normal, measured by the Bessey method, and to elevated but more variable values by the Sobel-Snow method. The serum carotene levels were unaffected by vitamin A administration. Retinol-binding protein levels from both cases rose slightly after one month of oral vitamin A (Figure 14).

Fundus photographs of Cases A-3 and B-5 were taken at the end of each period of oral vitamin A administration. A few of the punctate lesions changed during each trial of vitamin A, but the changes were similar to those which occurred over time alone (see Figure 4) and did not represent any net loss of lesions.

The visual acuity of both cases was stable throughout this study. After the initial month of oral vitamin A, the visual fields of Case A-3 showed the same mild defects that were present before, and both cases still made minor

color reversals with the Farnsworth D-15 color test. Dark adaptometry and ERG's were performed after each injection of vitamin A and each period of oral supplementation. The dark adaptation curves were continued for at least two hours after pre-adaptation to light, but no improvement could be detected in either patient (Figure 15). The ERG's were all recorded after 20 minutes of dark adaptation, first noting the b-wave threshold and then the response to a bright (W-8) flash for measurement of the a- and b-wave amplitudes and the b-wave implicit time. There was no clear effect of vitamin A on any of these ERG parameters (Figure 16).

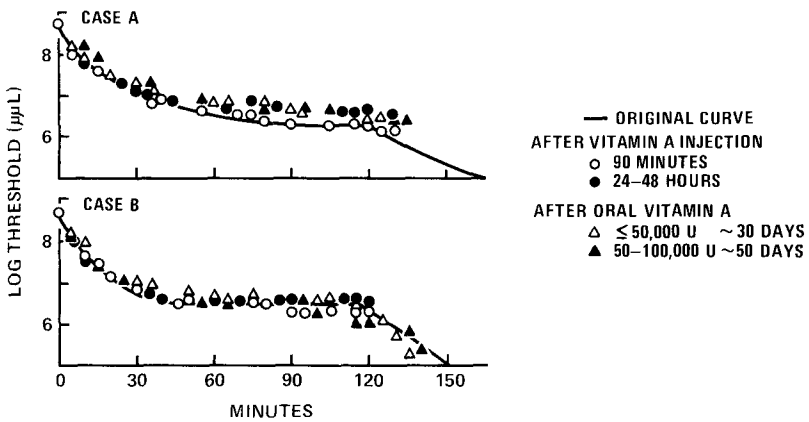

Fig. 15. Dark adaptation curves before and after vitamin A administration.

DISCUSSION

Fundus lesions

The nature of the whitish punctate lesions in fundus albipunctatus remains a mystery. They appear to be deep to the retinal vessels (see Figure 4), although cases have been described by others (e.g. Carr, et al., 1976) in which some of the spots appear superficial. The spots are not pigment epithelial defects since they do not transmit, and in fact may block, fluorescein during angiography (Figures 5 and 6). Carr et al. (1976) describe autofluorescence of the punctate lesions, but this was not evident in my patients. Independent of the spots, the pigment epithelium appears diffusely depigmented. The lesions in the present cases seem to reside in or near the pigment epithelium, perhaps representing material (as in fundus

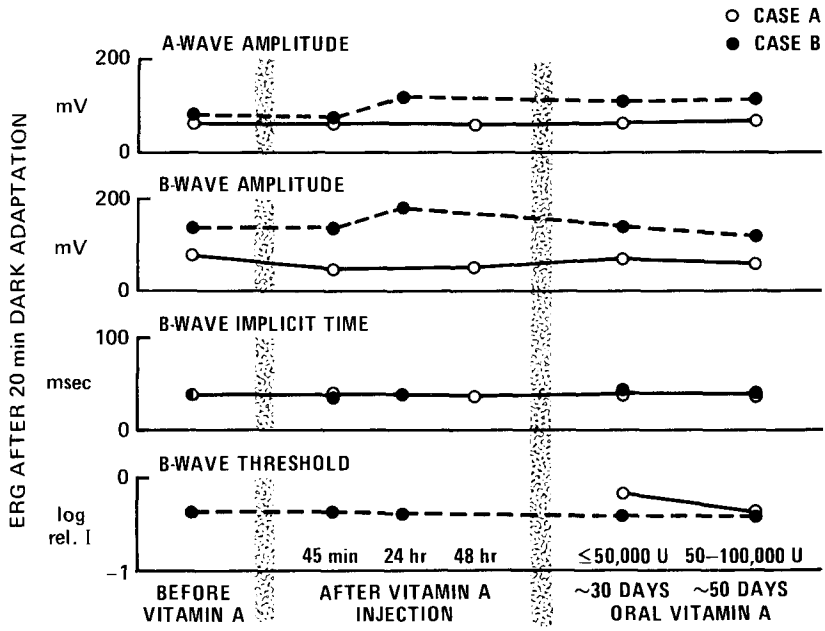

Fig. 16. ERG parameters before and after vitamin A administration. At each trial, the patient was dark adapted for 20 minutes after which the b-wave threshold and the response to a bright flash were recorded.

flavimaculatus – Klien & Krill, 1967) which can block fluorescence while accounting for generalized pigment epithelial damage.

The punctate lesions in Case A-3 show a striking radial pattern (Figure 2) which is visible in pictures from a few other cases (Krill & Klien, 1965; Carr, 1974; Carr et al., 1976) but has not been commented upon. The origin of this pattern is obscure, but it may be a clue to the nature of the disease even though it is not evident in all patients (including my Case B-5). The pattern does not follow the nerve fibers (which are, in any event, too superficial), or the visible retinal and choroidal vessels. Other unlikely vascular patterns include the choriocapillaris (which is segmentally, not radially, arranged – Hayreh, 1975) and the ciliary arteries (whose runoff zones radiate from the macula but show a 'watershed' effect not seen in the punctate lesions – Hayreh, 1975). Possibly the mosaic of pigment epithelial cells or photoreceptors accounts for the pattern.

Another feature of Case A-3's fundus, in contrast to Case B-5's, is the foveal abnormality, consisting of an absent light reflex and some mild sub-

foveal pigment dispersion. The presence of foveal pathology does not seem too surprising in a disorder that affects cone as well as rod function, but apparently the anatomic changes are not severe enough (at least at present) to affect visual acuity.

The lesions in fundus albipunctatus have been described as stable, including two cases followed for more than 35 years (Nettleship, 1914; Franceschetti & Chome-Bercioux, 1951). No photographic comparison has been published, however. Figure 4 shows that while most of the lesions are constant, a few dots have clearly faded and a few new ones have clearly appeared over a 1-2 year period. This flux of lesions is important because it may reflect a changing metabolic state that is amenable to analysis or therapy. Furthermore, the fact that some individual dots appear to be labile (i.e. come and go in the same location), suggests that anatomic factors may influence the site of lesions while other factors determine the presence of abnormal material.

The possibility that vitamin A deficiency causes or predisposes to albipunctate lesions is suggested by the similar lesions seen in some patients with vitamin A deficiency (Uyemura, 1928; Teng, 1965; Levy & Toskes, 1974) and abetalipoproteinemia (Gouras et al. 1971). The lesions in vitamin A deficiency are usually reversible with therapy, however, while vitamin A administration had no effect on fundus lesions in the present study. The albipunctate lesions also were not related to the state of dark adaptation, in contrast to Oguchi's disease in which an abnormal coloration of the light-adapted eye fades during dark adaptation (Carr, 1974). If vitamin A metabolism is involved in the production of the fundus albipunctatus lesions, the defect would appear to be at a cellular rather than systemic level (as discussed further below).

The change in appearance of the punctate fundus lesions beyond the vascular arcades is of interest. In the zone between the macula and equator, the lesions of both these patients appear more like flavimaculatus 'flecks' than 'albipunctate' lesions. Fundus flavimaculatus, of course, represents a very different syndrome characterized in many cases by macular degeneration (i.e. Stargardt's disease). However, occasional patients have been described (Klien & Krill, 1967; Franceschetti & Francois, 1965) with peripheral flavimaculatus and little or no functional deficiency except mildly abnormal dark adaptation. The lesson to be learned may be that visible lesions are not the best criteria for ophthalmic diagnosis. Physiologic parameters are far more definitive, and fundus albipunctatus should probably be defined on the basis of its functional deficit rather than the character of its fundus lesions (Marmor, 1977).

Physiologic defect

Fundus albipunctatus has generally been described as a recessively inherited night blindness. The two families reported here each have only one affected member who is the product of a consanguinous marriage (see Figure 1) so that autosomal recessive inheritance is most likely. Carr et al. (1974) showed by fundus reflectometry that visual pigment regeneration was abnormally slow in two brothers with fundus albipunctatus, and the rate of dark adaptation corresponded to the rate of pigment regeneration. The present study did not incorporate fundus reflectometry, and thus did not directly measure visual pigment regeneration. However, the physiologic findings in my patients are consistent with the conclusions of Carr et al.

First of all, the physiologic deficit in my patients may be localized prior to the generation of the a-wave, since the a-wave (as well as the b-wave) was absent from the ERG when the patients were insufficiently dark-adapted. An abnormality of dark adaptation which originates in the outer segments or pigment epithelium is consistent with an abnormality of the pigment regeneration cycle as opposed to one involving neural mechanisms of adaptation. Second, the state of dark adaptation (subjective or electrophysiologic) was unaffected by brief flashes of light that do not bleach a significant amount of rhodopsin (see Figure 11). This also suggests that retinal sensitivity was primarily dependent upon the amount of visual pigment rather than a neural factor as in Oguchi's disease, in which a single flash will light-adapt the eye (Gouras, 1970). Third, all of the ERG parameters that were measured (including b-wave threshold) developed changes during dark adaptation at the same rate as changes in subjective sensation, exactly as in a normal subject. This finding is suggestive of an adaptation defect that precedes the generation of the ERG and can account for both electrophysiologic and psychophysical sensitivity.

Fundus albipunctatus is often described as a night-blinding disorder, but the dark adaptation curves show that it is a disorder of cone dysfunction as well. In fact, cone dark adaptation is more prolonged than rod dark adaptation relative to the normal rates. Both of my patients complained of difficulty upon going from a bright to a dimly lit (but not necessarily scotopic) environment. For example, Case B-5 was discovered because she couldn't see well in a recreation area dressing room which must have had at least mesopic illumination. There have been only a few reports of photopic visual defects in this disorder (e.g. Aouchiche et al., 1969), but both of my patients showed subtle abnormalities. The visual fields were not quite normal, and color perception was mildly deficient especially in blue-yellow discrimination.

The range of clinical variation in fundus albipunctatus is unknown. My cases, and several others in the literature (Huber et al., 1957; Franceschetti et al., 1963; Carr et al., 1974; Carr et al., 1976) have severe defects in adaptation time. However, other patients have been reported to show only a mild prolongation of dark adaptation (Smith et al., 1959; Krill & Folk, 1962). A spectrum of severity may exist for expression of the adaptation defect or the mild cases may represent a distinct pathophysiologic entity. The degree of ERG abnormality has also varied considerably among reported cases, ranging from normal (Franceschetti & Dieterle, 1954; Franceschetti et al., 1963) to subnormal (Franceschetti et al., 1963; Franceschetti et al., 1974) to normal only after prolonged dark adaptation (Smith et al., 1959; Krill & Folk, 1962). These differences may, in part, reflect varying degrees of dark adaptation at the time of measurement.

In 1910, Lauber made a distinction between stationary and progressive forms of retinopathy characterized by white dots. However, there is no current unanimity about the clinical definition of fundus albipunctatus (cf. Aouchiche et al., 1969; Franceschetti et al., 1974) and whether or not it is related to retinitis punctata albescens. My own belief (Marmor, 1977) is that Lauber was fundamentally correct and that the demonstration of abnormal pigment regeneration in fundus albipunctatus by Carr et al. (1974) will serve as the definition of a discrete non-progressive condition. There is no fundus reflectometry evidence that progressive dystrophies such as retinitis punctata albescens or retinitis pigmentosa show retarded visual pigment regeneration, and in fact the few retinitis pigmentosa patients that have been studied showed a low density of rhodopsin in the dark-adapted state (Highman & Weale, 1973), and an unusually fast rate of pigment regeneration as inferred from the early receptor potential (Berson & Goldstein, 1970). There is also no evidence that patients with progressive dystrophies and impaired dark adaptation will ever reach a normal threshold, even if dark-adapted for extensive periods of time. Patients with retinitis punctata albescens typically have progressive symptoms (Case A-3 denies any progression over his 33-year lifetime); and they show narrowed retinal vessels, atrophic retinae, occasional pigment spicules, and in my experience, severe ERG changes which affect b-wave implicit time (cf. Berson et al., 1969) as well as amplitude. An occasional case may fall between the classic syndromes of fundus albipunctatus and retinitis punctata albescens, but ordinarily the distinction should not be difficult to arrive at with the aid of dark adaptometry and the ERG (fundus reflectometry is unfortunately not widely available). The most critical observation, often neglected in the literature, is a continuation of dark adaptometry beyond the routine 45 minutes to determine whether a normal threshold will ultimately be achieved.

A relationship between fundus albipunctatus and vitamin A metabolism is suggested by the abnormal visual pigment kinetics in fundus albipunctatus and by a resemblance to the syndrome of vitamin A deficiency. However, there is some question whether the dark adaptation defects in these two disorders are actually similar. Early studies on experimental vitamin A deficiency (Wald et al., 1938; Hecht & Mandelbaum, 1939) showed that, in contrast to fundus albipunctatus, cone and rod thresholds became elevated while the timing of the cone/rod break remained unaffected. On the other hand, delays in the cone/rod break were observed in patients who were vitamin A deficient because of alcoholic cirrhosis of the liver (Haig et al., 1938), and in the subjects of the cooperative British study who were on a vitamin A-free diet for more than a year (Hume & Krebs, 1949). The kinetics of dark adaptation in vitamin A deficiency may depend upon factors such as the duration or cause of deficiency which have not been adequately studied.

The present report shows that serum vitamin A, carotene and retinol binding protein were all normal in patients with fundus albipunctatus. Case B-5 showed a borderline level of vitamin A determined by the Bessey method, but this value is of doubtful significance since her normal parents also had low Bessey values on the same day, and all three blood samples were normal when analyzed by the Sobel-Snow method. Carr et al. (1976) also found normal vitamin A levels in a patient with fundus albipunctatus. Clearly, the disease cannot be explained simply on the basis of low systemic vitamin A levels or a deficiency of the transport protein. However, as Gouras & Chader (1974) have pointed out, qualitative abnormalities in the nature of the binding protein that would not be detected in this study could affect binding or release of vitamin A at the target tissue.

The blood and urine of these fundus albipunctatus patients were analyzed for substance other than vitamin A-related compounds that might relate to the retinal dysfunction. Chemical abnormalities have been found in several fundus dystrophies including abetalipoproteinemia (Salt et al., 1960), Refsum's syndrome (Steinberg et al., 1967) in which phytanic acid is elevated, gyrate atrophy (Takki, 1974) in which ornithine is elevated, and a feline maculopathy (Schmidt et al., 1976) in which taurine is deficient. However, all of these classes of compound were normal in my patients.

The signs and symptoms of vitamin A deficiency, including the white fundus lesions, are generally reversible with replacement therapy (Uyemura, 1928; Teng, 1965; Levy & Toskes, 1974). Vitamin A therapy also can partially reverse the dark adaptation and ERG abnormalities of abetalipoproteinemia (Gouras et al., 1971), although the long-term ability of vitamin

A to prevent progression of the dystrophy has been questioned. Replacement therapy was attempted with the present patients, who were not systemically deficient in vitamin A, to see whether loading with the vitamin might overcome a local deficiency and alter retinal function. The dosages used were comparable to those used in the treatment of vitamin A deficiency and abetalipoproteinemia, but were chosen to avoid any danger of hypervitaminosis (Korner & Vollm, 1975). Neither parenteral nor oral supplementation was found to have any effect on the fundus lesions or the rate of dark adaptation (measured subjectively or by the ERG). However, the vitamin A levels never rose much beyond normal, so the possibility remains that extremely high dosages might force an improvement. The treatment periods in this study were 27-55 days, and it is conceivable that longer treatment might have some effects.

These findings are disappointing insofar as no systemic abnormality or therapeutic effect of vitamin A was discovered. They are not surprising, however, since the clinical effects of fundus albipunctatus appear limited to the eye. If vitamin A metabolism is involved at all in fundus albipunctatus, the involvement is probably at a cellular level. Recent papers (e.g. Gouras & Chader, 1974; Zimmerman et al., 1974; Bergsma et al., 1976) have emphasized that complex mechanisms, which are largely independent of systemic vitamin A levels, mediate the binding, transport and metabolism of visual pigments in the photoreceptors and the pigment epithelium. The pigment regeneration cycle may also be affected indirectly by abnormalities of energy metabolism or of membrane permeability.

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REFERENCES

Aouchiche, M., Boyer, R. & Zetchi, A. De la difficulté du diagnostic entre la rétinopathie ponctuée albescente et le fundus albipunctatus cum hemeralopia. *Bull. Soc. Ophtalmol. Fr.* 82: *573–584* (1969).

Bergsma, D.R., Wiggert, B.N., Funahash, M., Kuwabara, T. & Chader, G.J. Vitamin A receptors in normal and dystrophic human retina. *Nature* 265: *66–67* (1977).

Berson, E.L. & Goldstein, E.B. Recovery of the human early receptor potential during dark adaptation in hereditary retinal disease. *Vision Res.* 10: *219–226* (1970).

Berson, E.L., Gouras, P. & Hoff, M. Temporal aspects of the electroretinogram. *Arch. Ophthalmol.* 81: *207–214* (1969).

Carr, R.E. Congenital stationary nightblindness. *Trans. Am. Ophthalmol. Soc.* 72: *449–487* (1974).

Carr, R.E., Ripps, H. & Siegel, I.M. Visual pigment kinetics and adaptation in fundus albipunctatus. XIth ISCERG Symp. Bad Nauheim 1973. Doc. Ophthalmol. Proc. Ser. 4: *193–204.* Junk, The Hague (1974).

Carr, R.E., Margolis, S. & Siegel, I.M. Fluorescein angiography and vitamin A and oxalate levels in fundus albipunctatus. *Am. J. Ophthalmol.* 82: *549–558* (1976).

Franceschetti, A. & Chome-Bercioux, N. Fundus albipunctatus cum hemeralopia. *Ophthalmologica* 121: *185–193* (1951).

Franceschetti, A. & Dieterle, P. Importance diagnostique et prognostique de l'electroretinogramme (ERG) dans les degenerescences tapeto-retiniennes avec retrecissement du champ visuel et hemeralopie. *Confin. Neurol.* 14: *184–186* (1954).

Franceschetti, A., Dieterle, P., Ammann, F. & Marty, F. Une nouvelle forme de fundus albipunctatus cum hemeralopia. *Ophthalmologica* 145: *403–410* (1963).

Franceschetti, A. & François, J. Fundus flavimaculatus. *Arch. Ophtalmol.* (Paris) 25: *505–530* (1965).

Franceschetti, A., François, J. & Babel, J. Chorioretinal heredodegenerations. Charles C. Thomas, Springfield pp. *222–250* (1974).

Gouras, P. Electroretinography: some basic principles. *Invest. Ophthalmol.* 9: *557–569* (1970).

Gouras, P., Carr, R.E. & Gunkel, R.D. Retinitis pigmentosa in abetalipoproteinaemia: Effects of vitamin A. *Invest. Ophthalmol.* 10: *784–793* (1971).

Gouras, P. & Chader, G. Retinitis pigmentosa and retinol-binding protein. *Invest. Ophthalmol.* 13: *239–242* (1974).

Gunkel, R.D. & Bornschein, H. Automatic intensity control in testing dark adaptation. *Arch. Ophthalmol.* 57: *681–686* (1957).

Haig, C., Hecht, S. & Patek, A.J. Jr. Vitamin A and rod-cone dark adaptation in cirrhosis of the liver. *Science* 87: *534–536* (1938).

Hayreh, S.S. Segmental nature of the choroidal vasculature. *Br. J. Ophthalmol.* 59: *631–648* (1975).

Hecht, S. & Mandelbaum, J. The relation between vitamin A and dark adaptation. *JAMA* 112: *1910–1916* (1939).

Highman, V.N. & Weale, R.A. Rhodopsin density and visual threshold in retinitis pigmentosa. *Am. J. Ophthalmol.* 75: *822–832* (1973).

Huber, V.O., Franceschetti, A. & Dieterle, P. Zur Differentialdiagnose zwischen Fundus albipunctatus cum Hemeralopia congenita und Oguchi'scher Krankheit. *Ophthalmologica* 133: *283–287* (1957).

Hume, E.M. & Krebs, H.A. Vitamin A requirement of human adults. *Med. Res. Counc. Spec. Rep. Ser.* (Lond.) 264: *1–145* (1949).

Klien, B.A. & Krill, A.E. Fundus flavimaculatus. *Am. J. Ophthalmol.* 64: *3–23* (1967).

Krill, A.E. & Folk, M.R. Retinitis punctata albescens. A functional evaluation of an unusual case. *Am. J. Ophthalmol.* 53: *450–455* (1962).

Krill, A.E. & Klien, B.A. Flecked retina syndrome. *Arch. Ophthalmol.* 74: *496–508* (1965).

Korner, W.F. & Vollm, J. New aspects of the tolerance of retinol in humans. *Int. J. Vitam. Nutr. Res.* 45: *363–372* (1975).
Lauber, H. Die sogenannte Retinitis punctata albescens. *Klin. Monatsbl. Augenheilkd.* 48: *133–148* (1910).
Levy, N.S. & Toskes, P.P. Fundus albipunctatus and vitamin A deficiency. *Am. J. Ophthalmol.* 78: *926–929* (1974).
Marmor, M.F. Corneal electroretinograms in children without sedation. *J. Pediatr. Ophthalmol.* 13: *112–118* (1976).
Marmor, M.F. Defining fundus albipunctatus. XIVth ISCERG Symp. Louisville, 1976. Doc. Ophthalmol. Proc. Ser. 13: 227–234. Junk, The Hague (1977).
Nettleship, E. A note on the progress of some cases of retinitis pigmentosa and of retinitis punctata albescens. *Roy. Lond. Ophthalmol. Hosp. Rep.* 19: *123–129* (1914).
Salt, H.B., Wolff, O.H., Lloyd, J.K., Fosbrooke, A.S., Cameron, A.H., & Hubble, D.V. On having no beta-lipoprotein. *Lancet: 325–329* (1960).
Schmidt, S.Y., Berson, E.L. & Hayes, K.C. Retinal degeneration in cats fed casein. I. Taurine deficiency. *Invest. Ophthalmol.* 15: *47–52* (1976).
Smith, B.F., Ripps, H. & Goodman, G. Retinitis punctata albescens. *Arch. Ophthalmol.* 61: *93–101* (1959).
Steinberg, D., Herndon, J.H. Jr., Uhlendorf, B.W., Mize, C.E., Avigan, J. & Milne, G.W.A. Refsum's Disease: nature of the enzyme defect. *Science* 156: *1740–1743* (1967).
Takki, K. Gyrate atrophy of the choroid and retina associated with hyperornithinaemia. *Br. J. Ophthalmol.* 58: *3–23* (1974).
Teng Khoen Hing. Further contributions to the fundus xerophthalmicus. *Ophthalmologica* 150: *219–238* (1965).
Uyemura, M. Ueber eine merkwurdige Augenhintergrundveranderung bei zwei Fallen von idiopathischer Hemeralopie. *Klin. Monatsbl. Augenheilkd.* 81: *471–473* (1928).
Wald, G., Jeghers, H. & Arminio, J. An experiment in human dietary night-blindness. *Am. J. Physiol.* 123: *732–746* (1938).
Zimmerman, W.F., Yost, M.T. & Daemen, F.J.M. Dynamics and function of vitamin A compounds in rat retina after a small bleach of rhodopsin. *Nature* 250: *66–67* (1974).

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