VISION IN ALBINISM

BY *C. Gail Summers*, MD

ABSTRACT

Purpose: The purpose of this investigation was to study vision in albinism from 3 perspectives: first, to determine the characteristics of grating acuity development in children with albinism; second, to study the effect of illumination on grating acuity; and third, to define the effect of melanin pigment in the macula on visual acuity.

Methods: I. Binocular and monocular grating acuity was measured with the acuity card procedure in 40 children with albinism during the first 3 years of life. Recognition acuity was eventually measured in 27 of these patients. Ocular pigment was documented by a previously established method of grading iris transillumination and macular transparency.

II. Grating acuity under standard and increased illumination levels was measured in 20 adults with albinism (group I) and compared with that in 20 adults with nystagmus due to conditions other than albinism (group II) and 20 adults without ocular abnormalities (group III). Recognition acuity measured with the ETDRS charts was also recorded for each group.

III. Best-corrected binocular acuity was measured in 29 patients with albinism who were identified with melanin pigment in their maculas by direct ophthalmoscopy.

Results: I. Both binocular and monocular grating acuity was reduced 2 to 3 octaves below the norm for ages 6 months to 3 years. Limited data available in the first 6 months of life did not show failure of vision to develop. Grating acuity measurements overestimated eventual recognition acuity. Mean recognition acuity was 20/111. A relationship between grating acuity development and presence or absence of ocular pigment was not found.

II. Grating acuity was significantly better for groups I and II under the condition of increased illumination ($P < .03$). For patients with albinism, grating acuity under standard illumination was significantly better than recognition acuity ($P < .001$). For all groups, grating acuity under increased illumination was significantly better than recognition acuity ($P < .01$).

III. Mean recognition acuity in patients with albinism and melanin pigment in their maculas (20/47) was significantly better than measured recognition acuity in Project I ($P < .001$). All had foveal hypoplasia, but 8 patients had an incompletely developed annular reflex in the macula, 6 patients showed stereoacuity, and 3 patients had no nystagmus.

Conclusions: I. Grating acuity development in albinism seems to progress along a curve that is asymptotic to visual development in a normal population.

II. Increasing illumination does not reduce grating acuity in patients with albinism. Grating acuity overestimates recognition acuity in these patients.

III. Ophthalmoscopic detection of melanin pigment in the macula in patients with albinism is associated with better vision.

INTRODUCTION

Albinism, derived from the Latin, *albus*, meaning white, refers to congenitally absent or reduced melanin pigment in the eyes, and often hypopigmentation in the skin and hair as well. When a child develops nystagmus within the first few weeks of life and examination discloses iris transillumination, foveal hypoplasia, and a blond fundus, a diagnosis of albinism may be suspected. Family history is often negative, as this disorder is inherited in a recessive manner, most commonly autosomal recessive, except in males with predominantly ocular hypopigmentation, where the inheritance may be X-linked.

Melanin biosynthesis occurs in the melanosome that is localized within specialized dendritic cells, called melanocytes. These melanocytes are normally found in skin, hair follicles, meninges, and inner ear in addition to the uveae and retinal pigment epithelium. Melanosomes are divided into 4 types according to their structural architecture. Premelanosomes (types I and II), formed from the Golgi complex, are progressively filled with membranous structures and enzymes, and eventually with melanin, to produce more mature melanosomes (types III and IV). All types of melanosomes, without melanin pigment, have been identified in the iris from 2 patients with tyrosinase-negative albinism.[1,2] Melanocytes originating from the neural crest in embryonic development migrate to the iris stroma and choroid, whereas melanocytes in the pigment epithelium of the iris and retinal pigment epithelium originate from the neuroectodermal outer layer of the optic cup. With normal maturation, melanogenesis increases, modified by environmental and genetic factors. Compared with cutaneous melanocytes, which are derived from the neural crest, the neu-

roectodermally derived melanocytes in the eye do not transfer their pigment to adjacent cells and do not continue to synthesize new melanin. Tyrosinase is the first enzyme in the pathway to convert tyrosine into melanin and catalyzes the rate-limiting step in melanin biosynthesis. Although melanocytes and melanosomes are present in the skin, hair follicles, and eye in persons with albinism, the melanosomes may contain no melanin or a reduced amount of melanin. Reduced or absent tyrosinase activity due to mutant alleles of the tyrosinase gene is a frequent cause of oculocutaneous albinism (OCA).[3] Other enzymes or regulatory factors involved in the later steps in melanin synthesis produce other patterns of hypopigmentation in albinism.

This thesis will first provide an overview of the current classification of albinism and the specific ocular features of this genetic disorder. This discussion is followed by the presentation of three different projects that present new information regarding vision in albinism.

CLASSIFICATION OF ALBINISM

Albinism occurs with an overall frequency of 1 in 18,000 in the United States.[4] In the past, the terms "complete" and "partial" albinism or "perfect" and "imperfect" albinism were used to describe the amount of pigment that was clinically apparent in the heterogeneous expression of the phenotype. The presence or absence of pigmentation detected with incubation of hairbulbs in tyrosine or DOPA initially was used to establish the division of oculocutaneous albinism into tyrosinase-negative and tyrosinase-positive types. Further studies of hairbulb tyrosinase activity were helpful in defining the type of albinism and in understanding the variable phenotype in both individuals with OCA and in heterozygotes.[5-8] However, as clinical, biochemical and molecular studies have progressed, the currently evolving classification schema describes albinism on the basis of the genetic defect. OCA type 1 (OCA1) refers to a clinical picture of hypopigmentation resulting from mutations of the tyrosinase gene on chromosome 11q14-21,[3] causing either complete absence ("tyrosinase-negative" albinism, OCA1A) or some residual activity (OCA1B, OCA1MP, OCA1TS) of the encoded enzyme. The defective gene in the other common type of albinism ("tyrosinase-positive" albinism, OCA2) codes for a transmembrane protein that has been mapped to chromosome 15q11.2-12; these individuals are typically born with melanin pigment in their hair, in contrast to the white hair that is present at birth in OCA1. The gene in OCA2 has been referred to as the "P gene," as similar clinical and genetic features are found in the pink-eyed-dilution (p) mouse. There are also other unclassified types of pigmenting albinism, such as Brown OCA,

which has been reported in African, African American, and Caucasian populations. Finally, OCA may be a secondary association occurring with systemic disorders such as Hermansky-Pudlak syndrome (chromosome 10) and Chediak-Higashi syndrome. In all cases, the inherited deficiency is in the production of melanin pigment. Red (rufous) OCA has been reported in patients from South Africa, but only 1 patient had nystagmus, none showed foveal hypoplasia, and misrouting of the optic fibers measured by visual evoked potentials was not found.[9] This disorder remains poorly defined as a specific type of OCA. Autosomal dominant OCA has also been reported, but it has been incompletely characterized as a specific type of OCA.[10,11] Ocular albinism (OA) is less commonly noted than OCA, and affected individuals will have reduced melanin pigment primarily in the eyes.[12] Inheritance of OA may be either autosomal recessive or X-linked recessive (OA1).

TYROSINASE-RELATED ALBINISM (OCA1)

In tyrosinase-related albinism, a variable presence or absence of melanin pigment production is noted, depending on the effect of the mutation in the tyrosinase gene.[3] Most affected individuals are compound heterozygotes with different maternal and paternal mutant alleles. Patients who are unable to produce melanin pigment have the classic "tyrosinase-negative" phenotype, while others who have different mutations of the tyrosinase gene have some residual enzyme activity and are able to form some pigment.

In tyrosinase-negative albinism (OCA1A, Type IA, McKusick 203100.0001-203100.0005, 203100.0010-203100.0011, 203100.013-203100.0036), melanin pigment is not present in the hair, skin, or eyes at birth, nor does it develop throughout life, irrespective of ethnic origin. The hair is white, and the skin is white and does not tan. There is no ocular melanin present in these individuals, and they typically have pink, translucent irides owing to the complete absence of melanin pigment in both the posterior iris epithelium and the iris stroma. With biomicroscopic examination, a small light is directed through the pupil, and the entire iris is illuminated as a reddish-orange color. The iris vasculature and the edge of the lens can easily be identified owing to the complete iris transillumination. Examination of the fundus shows absence of melanin pigment and foveal hypoplasia. Individuals often have coarse nystagmus and photophobia, and best-corrected vision is reduced to 20/200 to 20/400.[13,14] They may develop a compensatory head posture to dampen their nystagmus and afford them the best vision. Various mutations of the tyrosinase gene on chromosome 11q14-21 have been reported in OCA1 A.[15-19]

Other types of tyrosinase-related albinism encompass a group of patients in whom melanin pigment in the eye, skin, and hair is absent at birth, but then develops in variable amounts, owing to mutations of the tyrosinase gene encoding an enzyme with residual function.[20] In one of these groups—Yellow OCA (OCA1 B, McKusick 203100.0006-203100.0007), characterized by the eventual development of yellow or blond hair—melanin pigment is absent at birth, but pheomelanin and eventually eumelanin develop in the scalp hair as the individual matures.[21] Although individuals at birth appear to have OCA1A, the developing clinical phenotype is variable in Yellow OCA, apparently related to ethnic influence and the amount of residual tyrosinase activity. Some individuals with this type of OCA1 actually form nearly normal amounts of hair and skin pigment as they develop and may appear to have autosomal recessive ocular albinism. Vision is variably reduced, with one study[13] noting a mean acuity of 20/200 for 7 patients with Yellow OCA. Some pigment can usually be detected in the iris with biomicroscopic examination.[14] Mutations in the tyrosinase gene have been described.[22] Also included in OCA1 with residual enzyme activity are the unusual presentations of the "minimal pigment" type of albinism (OCA1MP, previously called Type III, McKusick 203280) and "temperature-sensitive" albinism (OCA1TS, McKusick 203100.0012). In OCA1MP, absent cutaneous and hair pigment is noted in the first few weeks of life, but older individuals have heterogeneous phenotypes.[23] All have nystagmus and foveal hypoplasia, with a recent report of 9 patients noting vision between 20/50 and 20/200.[24] Some individuals with OCA1MP may develop iris pigment detected with biomicroscopy. Diagnosis is made when these features of OCA are associated with low hairbulb tyrosinase activity in the affected individual and one parent, with the other parent having normal activity. In the rare individual with temperature-sensitive albinism, residual tyrosinase enzyme activity increases with decreasing temperature, producing white hair on the warmer portions of the body (axilla and scalp), with pigmented hair developing on the cooler parts of the body (arms and legs), similar to the Siamese cat.[12,25] This is due to a missense mutation in the tyrosinase gene, resulting in the production of a tyrosinase polypeptide that is temperature-sensitive.[26] A patient with OCA1TS has been reported with 20/200 vision, nystagmus, foveal hypoplasia, and absence of ocular melanin pigment.[27] Individuals with OCA1MP and OCA1TS are usually compound heterozygotes, having two different abnormal tyrosinase alleles.

As more molecular information becomes available, it appears that OCA1 represents a spectrum of phenotypes from absence of skin, hair, and eye pigment to nearly normal adolescent and adult skin and hair pig-

ment. This spectrum is the result of tyrosinase gene mutations that are associated with variable amounts of residual enzyme function. No tyrosinase function at this critical stage of melanin synthesis leads to a life-long lack of melanin production, whereas increasing amounts of residual enzyme function will be associated with increasing amounts of melanin formation. It is not always possible to identify particular patients with OCA1B or OCA1MP, as they are part of the OCA1 spectrum with varying phenotypes.

OCA2

In contrast to OCA1, melanin pigment is present in the hair and eye at birth and develops in the skin in OCA2 (Type II, tyrosinase-positive albinism, McKusick 203200.0001, 203200.004-203200.006). In these individuals, tyrosinase activity is normal and deficient melanin pigment results from defective synthesis or function of a transmembrane protein that is required for melanogenesis. These individuals show varying phenotypes, related in large part to their ethnic background.[28] A variable degree of iris transillumination is present owing to variable amounts of melanin pigment in the posterior iris epithelium and in the iris stroma. It has been suggested that, with increasing age, pigment gradually accumulates in this type of albinism, first at the pupillary border.[14,28] Although vision is often better in OCA2 than in OCA1, the characteristic features of nystagmus, foveal hypoplasia, and misrouting of the retinofugal pathways are common to both.[13]

BROWN OCA

First identified in Nigeria, individuals with Brown OCA (Type IV, McKusick 203290) readily tan and have more melanin pigment in their skin and hair than most individuals with albinism, but less pigment than their normally pigmented family members.[29,30] More recently, King and associates[31] have presented the clinical findings in 7 patients with Brown OCA who were seen in the United States. Since these patients had more pigment in their hair, skin, and eyes than is usually associated with OCA in the United States, their previous diagnoses included congenital nystagmus or disorders of the retina other than albinism. Electron microscopy of hair-bulbs and skin showed a reduced number of mature stage IV melanosomes, accounting for the reduced pigmentation. Best-corrected visual acuity varied from 20/60 to 20/150. Myopia greater than 7.50 diopters was noted in 3 of the 7 patients. Interestingly, only 1 of the 7 patients with Brown OCA seen in the United States was noted to have strabismus, and this was successfully corrected with extraocular muscle

surgery. Stereoacuity was not reported in this series, and all patients had nystagmus. Clinical examination of the fundus showed some melanin pigment accumulation and a "muted" foveal light reflex. The characteristic absence of both an annular depression in the macula and normal vascular wreathing of the macula is seen in an accompanying fundus photograph.[31] Thus, despite an increased amount of melanin pigment detected with examination of the fundus, normal macular and foveal architecture did not develop in these patients.

SECONDARY OCA

Finally, unusual forms of OCA may be associated with systemic conditions that often are more serious than the amount of hypopigmentation. These include Hermansky-Pudlak syndrome (HPS) (McKusick 203300) and Chediak-Higashi syndrome (CHS) (McKusick 214500), both of which are inherited as autosomal recessive disorders. In both conditions, visual acuity is variable.[32-38] A previous study of 20 patients with HPS showed that best-corrected Snellen acuity ranged from 20/60 to 20/400 and all had nystagmus, but a correlation with the variable amount of iris transillumination was not found.[37] Interestingly, 5 of these reported patients had anterior displacement of Schwalbe's line, and 2 patients had microcornea. In another report of 55 patients with HPS,[38] vision ranged from 20/50 to 5/200, 15 had posterior embryotoxon, and 4 had Axenfeld's anomaly. Axenfeld's anomaly has been reported in other types of albinism, and the relationship between anterior segment abnormalities and albinism may be more than coincidental, and is perhaps related to deficient pigment during ocular development.[39-44] All 11 patients with HPS who had visual evoked potentials performed showed abnormal decussation of the retinostriate fibers.[37] Occurring most often in the Puerto Rican population, cutaneous hypopigmentation is also variable in HPS.[38,45] Diagnosis of this disorder, made by absence of dense bodies in platelets, is essential to alert the physician to the associated findings of excessive bleeding due to abnormal platelet aggregation, particularly with administration of aspirin, and pulmonary fibrosis and inflammatory bowel disease due to deposition of a ceroid-like material in the reticuloendothelial system, lung, and gastrointestinal mucosa.[38,46-55]

Increased susceptibility to bacterial infections is found in CHS, in addition to the typical findings of OCA.[56-57] The hair has a characteristic metallic gray color, and reduction in visual acuity is variable; ocular findings are often subtle, as these individuals frequently have a moderate amount of melanin pigment in their eyes.[32,58] Leukocytes contain giant cytoplasmic granules, suggesting a membrane defect.[59] Individuals with

CHS who survive the recurrent infections typically develop cranial and peripheral neuropathies[60] and serious lymphoreticular infiltration.[4]

OCULAR ALBINISM

Individuals with OA typically have some ocular pigment and often have better vision than is found in patients with OCA, although other ocular features are similar.[61] Ocular albinism is divided into 2 types according to the inheritance pattern: autosomal recessive OA (McKusick 203200.0002, 203310, OA3), occurring equally in males and females, and X-linked OA (OA1, Nettleship-Falls OA, McKusick 300500), with symptoms occurring primarily in males[44,62-64] and the gene having been mapped to the short arm of the X chromosome (p22.3 region).[65-67] One patient with OA3 has been found to have a deletion on the long arm of chromosome 6, but the significance of this for pigmentation is not known.[68] Another X-linked disorder described in the Åland Islands was referred to as OA2, but routing of the optic fibers was subsequently found to be normal, in contrast to the excessive decussation that is characteristic of albinism.[69] Recent studies of patients with presumed autosomal recessive OA (OA3) have shown that some have mutations of the tyrosinase gene, suggesting that some of these patients actually have OCA1.[70]

Although cutaneous pigment is generally normal in OA1, hypopigmented macules may be present, and giant melanosomes are found in both cutaneous and ocular melanocytes, suggesting that the defect in pigmentation is not confined to the eye.[71] Skin biopsies showing these giant pigment granules, which are up to 10 to 12 times the size of normal melanosomes, can be helpful in making the diagnosis of X-linked OA in either individuals with the typical ocular features of albinism or the presumed female carrier for OA1.[72] The biopsy specimen requires serial sectioning to avoid missing the enlarged pigment organelles.[71,73-75] Similar findings have also been noted in hairbulbs.[73] Large melanin granules also have been reported in CHS, although they are not identical to those associated with OA1.[59,76-78]

The obligate heterozygotes in autosomal recessive OA have no ocular or cutaneous abnormalities. However, the mother who carries the gene for X-linked ocular albinism typically has variable ocular findings but only rarely has symptoms.[74,75,79-83] Careful ophthalmic examination of the obligate carrier for X-linked OA discloses some areas of iris transillumination and/or areas of hyperpigmentation in the fundus in 80% to 90% of heterozygotes.[75,84-87] This pigmentary mosaicism in the fundus is a clinical manifestation of lyonization effect or X inactivation, where 1 of the maternal X chromosomes has the ability to produce normal pigment and the other X chromosome carries the gene for deficient melanin synthesis.

OPHTHALMIC FEATURES OF ALBINISM

REDUCED VISION

One of the most disabling features of albinism is the reduced vision that these individuals typically demonstrate. Anecdotal reports[88,89] suggest that visual maturation may be delayed in children with albinism, but it is not clear whether visual development progresses normally to a point where it is then arrested at a level determined by the potential for that particular individual, or, alternatively, visual development is delayed from birth and proceeds at a reduced rate until the full potential is reached. Visual acuity is variably reduced in albinism, depending in part on the type of albinism and amount of ocular melanin pigment.[12,13,44,61,90] Reports of vision vary from 20/20 to 20/400,[61,91,92] but frequently vision is reduced to 20/100 to 20/200.[3,13,93,94] A study of the nystagmus low retinal slip velocities in patients with albinism suggests that factors other than nystagmus account for the limited visual resolution.[95] The reduction in vision may be due, in part, to the constant association of foveal hypoplasia and associated structural and anatomical alterations of the foveal cone photoreceptors.[1,96-98]

High refractive errors are not unusual, and even with glasses, vision may not improve to a level at which a driver's license can be obtained.[14,37,44,61,81,94,99,100] However, many persons with albinism do well in school with preferential seating and can experience some improvement in vision with optical correction of their refractive error. Spectacles may be tolerated better when used to correct a large amount of hyperopia, compared with correction of myopia or astigmatism.[101] Only rarely do spectacles actually reduce visual acuity; this is related to distortion caused by viewing the visual target through the periphery of the spectacle lens when a marked head turn is required to dampen the associated nystagmus.[37] Contact lenses either for refractive correction or for limiting the amount of light reaching the retina have not been shown to be preferable over glasses.[93,94,102] As children with albinism mature in the educational system, they face increased visual demands and smaller print size, and they can benefit from bifocals, low-vision aids, or enlarged print.[12,61,94,99,100,102]

Many persons with albinism learn to adopt a compensatory head posture where the amplitude of nystagmus diminishes and vision improves. Some will show a reduction in the amplitude of their nystagmus over time, and this may contribute to a subjective improvement in vision. At times, individuals with albinism are also noted to have a head tremor or nodding with visual fixation, but the significance of this for vision and its relationship, if any, to nystagmus are unknown.[37,81,84]

Visual acuity in the adult with albinism varies, and clinical observa-

tions suggest that vision is related, in part, to the amount of melanin pigment that develops in the eye.[24] Previous reports have shown that some individuals with albinism have almost normal vision.[91,92,103] Because family members with albinism can have varying amounts of reduction in visual acuity, these "atypical" individuals are often discovered only with routine examination of relatives of a patient with the more typical features of albinism, including reduced vision. The findings of iris transillumination, foveal hypoplasia, reduced stereoacuity, and misrouting of the optic fibers allow the diagnosis of albinism to be made in these individuals with almost normal visual acuity. Another patient with blond hair, nystagmus, and visual acuity of 20/25 monocularly and 20/20 binocularly was diagnosed with tyrosinase-related albinism only when molecular analysis disclosed 2 mutations of the tyrosinase gene.[103] As molecular analysis becomes more readily available, accurate diagnosis of albinism, as well as the specific type of albinism, may be more easily ascertained.

Color vision is usually normal or only mildly abnormal in albinism.[64,73] An increased number of errors without a specific axis have been found with the Farnsworth-Munsell 100-hue test, and widening into the red portion of the Rayleigh equation using the Nagel anomaloscope has been reported.[104,105] Such may be related to the decreased density of cones and absence of a rod-free zone within the macula of patients with albinism, in addition to associated abnormalities in neural circuitry.[1,96,97,105]

PHOTOSENSITIVITY

Another common, although not universal, finding in albinism is photosensitivity or photoaversion, and parents often report that their children with albinism squint or close their eyes when exposed to bright light, beginning in infancy. Increased light scattering in eyes of individuals with albinism is reported and has been felt to reduce image contrast.[106] However, the degree of ocular pigment is not always correlated with the subjective report of photosensitivity.[37,38] Although photosensitivity in albinism probably represents reduced filtering of light by the deficient ocular melanin pigment,[106] photophobia has also been reported in other retinal disorders, such as Leber's congenital amaurosis and cone dystrophy where pigment is not deficient.[107] A bonnet, cap, or visor can help to shield the eyes from the sun, and some persons with albinism prefer tinted or shielded spectacles to reduce the sun sensitivity.[12,14,101,102,108,109]

STRABISMUS

Strabismus is a frequent finding in albinism, with both horizontal and vertical deviations being noted.[13,81,94,102] The unusual associations of OCA with

Duane's syndrome and the marked V-pattern esotropia that is characteristic of Apert's syndrome have also been reported.[110,111] Since the strabismus is present in childhood, individuals with albinism do not typically note diplopia. Despite the high frequency of strabismic deviations, amblyopia – or the need for optical penalization or pharmacologic therapy – is not frequently noted, and most often the reduction in reported visual acuity is symmetric.[38] One report has noted improvement in vision in an esotropic eye of a patient with albinism following spectacle correction and occlusion therapy.[112] Even though strabismic amblyopia appears to be unusual in persons with albinism, it has been suggested that bilateral meridional amblyopia can develop owing to the presence of primarily unidirectional nystagmus that is present from an early age.[113]

When large-amplitude nystagmus coexists in patients with strabismus, as is typical of individuals with albinism, accurate measurement of the angle of misalignment can be difficult. Individuals with albinism and esotropia may have the appearance of orthophoria on casual gaze owing to the presence of positive angle kappas.[37] A rapidly performed alternate prism cover test, however, may quantify the strabismus.[37] Similarly, those with larger esodeviations measured by alternate prism cover may appear to have smaller deviations by Krimsky measurement. Thus, since patients with albinism typically do not have the topographic anatomy required for cortical binocularity, and their alternate prism cover measurements are typically different from Krimsky measurements, planning for extraocular muscle surgery may be best determined by the Krimsky measurement instead of the more frequently used alternate prism cover test. For exodeviations that appear greater with Krimsky measurements than alternate prism cover measurement, preoperative use of corrective prism can alert the clinician to the potential for diplopia following strabismus surgery that is performed for the Krimsky measurement.

IRIS TRANSILLUMINATION

Because of deficient melanin pigment in the iris stroma and posterior iris epithelium, light reflected from the retina is not filtered, and individuals with albinism can show pink, diaphanous-appearing irides. One method of quantifying iris translucency (QUIT) in albinism has been described by Wirtschafter and associates.[114] A neutral density filter is placed between the observer and the pupil of the eye, so that brightness of reflected light is equalized between the pupil and the iris. This technique uses a fiberoptic transilluminator held on the lower lid and an observer distance of 25 cm. Another study used contrast detection to determine light scattering through the iris in individuals with albinism, by directing a 1-mm^2 spot of

incandescent light toward the midposition on the inferior iris.[106]

A more popular method that is currently used to assess iris translucency uses the slit-lamp biomicroscope. With slit-lamp biomicroscopy, the examiner can frequently detect transillumination defects even in individuals without obvious iris translucency detected on casual gaze or with use of an external transilluminator. After the examiner has become accustomed to the dim illumination in the examining room, a small beam of light from the slit-lamp biomicroscope is directed through the pupil. The orange-appearing transillumination defects may be scattered and punctate, or diffuse transillumination of an iris with minimal or no pigment may be noted. A grading scheme for recording iris transillumination with slit-lamp biomicroscopy using a reference set of standard photographs has been recently published: grade 1, representing a marked amount of pigment in the posterior iris epithelium and the finding of punctate transillumination defects; grade 2, with a moderate amount of iris pigment and a greater amount of transillumination; grade 3, showing a minimal amount of iris pigment, often located in the iris stroma at the level of the collarette and almost complete iris transillumination; and grade 4, in which there is full iris transillumination and visualization of the edge of the lens due to complete absence of iris pigment.[37] A similar descriptive grading of iris translucency has been used to document the iris pigment in obligate heterozygotes for OA1.[75] Another report graded iris transillumination by number of degrees (90° to 360°) of involvement.[74]

NYSTAGMUS

Nystagmus in albinism, typically horizontal in direction and pendular or jerk in character, can be a cosmetically noticeable abnormality in affected persons, particularly early in life.[115-119] It has been suggested that the characteristics of the nystagmus may vary among types of albinism and thereby influence visual acuity.[118] Often persons with albinism learn to adopt a compensatory head posture to take advantage of the reduced amplitude associated with the null point, to improve vision. In addition, analysis of the nystagmus waveforms in patients with albinism has shown improved visual acuity with increased duration of low retinal slip velocities.[95] Although nystagmus in albinism is thought to be congenital, it may not be apparent at birth, but rather develops within a few days to several weeks following birth,[14,90,120-122] and may disappear as melanin pigment accumulates.[123] Occasionally, adult patients with albinism have noted oscillopsia with visual fixation.[37] This subjective response may be related to a change in the character of the nystagmus with intensive visual effort. Some investigators have suggested that continuous movement of the retinal image

owing to nystagmus is the primary optical reason for the degraded retinal image.[106] Interestingly, some patients with otherwise typical ocular features of albinism, including asymmetry of retinostriate projections with visual evoked potentials, will have no nystagmus that can be clinically detected even with scleral search coils.[91,92,115,124] These patients with albinism typically have normal, or nearly normal, vision.

When a significant head turn develops to dampen the nystagmus, horizontal extraocular muscle surgery (Kestenbaum-Anderson procedure) can be performed to allow the null point to be shifted to a position closer to primary gaze, to broaden the minimal intensity zone, and to decrease the overall nystagmus intensity, with some improvement in vision being noted.[125-129] More recently, retroequatorial placement of all 4 of the horizontal rectus muscles has been reported to reduce the amplitude of nystagmus and provide some improvement in at least subjective vision, even in patients with albinism and foveal hypoplasia.[130,131] This appears to be related to an increase in "foveation" time or prolongation of the low-velocity portion of the nystagmus waveform,[132] but improvement in visual acuity is often only modest. However, even a couple of lines of improvement in visual acuity can dramatically affect a person's lifestyle, particularly if it allows the individual to receive a driver's license. Although large recessions of the horizontal recti do not seem to significantly limit ocular motility, the long-term effects of such surgery are unknown. The amount of extraocular muscle surgery for both the Kestenbaum-Anderson procedure and the retroequatorial recession procedure can be adjusted to simultaneously improve any notable strabismus.

FUNDUS HYPOPIGMENTATION, FOVEAL HYPOPLASIA, OPTIC NERVE HYPOPLASIA

A common observation in individuals with albinism is the "blond" fundus due to the absence of melanin pigment in the retinal pigment epithelium and choroid. Choroidal vessels are easily visible in the retinal periphery and can often be seen in the macula. The transparency of the macula varies among individuals, but the reason for this is not clear.[133] A grading scheme for macular transparency has been previously published, ranging from grade 1, with easily visible choroidal vessels, to grade 3, in which the choroidal vessels are not ophthalmoscopically detectable in the macula.[37]

Foveal hypoplasia and reduced vision occur not only in association with rod monochromatism and aniridia, but also as an isolated finding and in association with other ocular abnormalities not related to albinism.[134-141] However, albinism is the most common reason for these findings on ophthalmic examination. Inspection of the fundus of persons with albinism

typically shows loss of the annular and foveal reflexes in the macula. Interestingly, despite the invariable appearance of foveal hypoplasia in albinism, visual acuity varies from 20/20 to 20/400.[13,71,73,91,92,94,124] Although angiographic study in 7 patients with albinism showed only mottling of the pigment epithelium, the normal "wreathing" of the macula by the retinal vessels is frequently reported to be absent, and, in fact, the retinal vessels can be disordered and may course directly through the expected area of the fovea.[14,37,73,133,142] Lack of foveal differentiation, the absence of a rod-free zone in the macula, decreased central cone density, and absence of typical cylindrical foveal cones have been reported with histopathologic examination of eyes from humans with X-linked OA and tyrosinase-negative OCA.[1,71] Spedick and Beauchamp[143] have observed small optic discs in patients with albinism and noted the similarity of macular and optic nerve findings between albinism and aniridia.

Although light filtering is reduced in the eyes of patients with albinism, electroretinography (ERG) has not documented deteriorating retinal status related to the toxic effects of light exposure. Rather, ERG recordings are frequently normal or occasionally supranormal.[36,64,73,88,92,107,144,145] It is debated whether the supranormal ERG responses are related to intraocular illumination with light passing through the scleral wall that has deficient melanin pigment, a greater scattering of light, or other factors.[144-146] Only rarely has the ERG been reported to be abnormal in albinism. A mildly subnormal scotopic ERG in 3 patients with autosomal recessive OA was thought to be related to associated myopia.[64] Although 2 patients with HPS, aged 14 and 48 years, had abnormal scotopic and photopic ERGs, suggesting a relationship to the known ceroid-lipofuscin accumulation in this disorder, another patient with HPS, aged 16 years, had a normal ERG.[35,147] With another electrophysiologic test, electro-oculography, a normal ratio has been found in individuals with albinism.[148]

MISROUTING OF OPTIC FIBERS

Although normal mammals have a varying, species-specific percentage of optic fibers that cross at the chiasm, visual pathways in albino animals are known to be uniformly aberrant.[94,149,150] In normally pigmented humans, about 53% of the retinal fibers decussate at the chiasm.[151] However, in human albinism, the abnormal chiasmic decussation of the retinal ganglion cells includes the posterior 20° of the temporal retina, leading to an abnormal arrangement of fibers in the lateral geniculate and an altered representation of the eye in the visual cortex. This excessive decussation can be detected with monocular pattern stimulation recorded with elec-

trodes placed on the scalp over the occiput.[152] The visual evoked potential that is designed to document the excessive decussation of the retinostriate fibers at the chiasm can be helpful in ascertaining a diagnosis of albinism, as this finding appears to be universal, regardless of the type of OA or OCA.[122,153-157] Even individuals with secondary OCA due to HPS and CHS show occipital hemispheric asymmetry that is distinctly different from normally pigmented individuals when monocular visual evoked potentials are examined.[37,158]

Although some investigators have had difficulty in recording the misrouting in patients with albinism, careful attention to methodology and type of stimulus, in addition to observation of the interocular hemispheric asymmetry detected with pattern onset-offset visual evoked potentials, permit differentiation of patients with albinism from patients with other diagnoses.[152,159] Despite this extensive topographic rearrangement of the retinocortical fibers in albinism, the aberrant configuration cannot be detected with magnetic resonance imaging.[160] The functional significance of this misprojection is probably related to the absence of stereovision that is typically present in albinism[94,161] and may also be related to the oculomotor abnormalities.[115]

The origin of the abnormal decussation of retinostriate fibers may be related to a reduction of melanin during embryogenesis.[162-164] In embryologic studies of mice, rats, chicks, and *Xenopus*, Silver and Sapiro[165] have demonstrated that the presence or absence of melanin pigment in the primitive eye stalk directs the migration of optic axons as they project posteriorally, thus offering an explanation for the topographic alteration of the optic tracts in albinism. Strongin and Guillery[166] have noted that degeneration of melanosomes near the junction of the optic cup and optic stalk in several mammalian species may play a role in ocular development. In addition, female mice with mosaicism due to X-autosome translocation have shown a variable pattern of decussation, possibly due to variability in either the gene dosage or the extent of the translocation.[167] In contrast to these studies, Colello and Jeffery[168] found no relationship between melanin in the optic stalk and routing of the optic tracts in rats.

When a diagnosis of albinism is suspected but the clinical features are not always characteristic (eg, nystagmus may be absent, but foveal hypoplasia is present and there is some reduction in melanin pigment in the retinal pigment epithelium), detection of this unique misrouting can be helpful. A visual evoked potential to detect this abnormal projection has been particularly useful in families who have variable expression of albinism among its members. There are reports of families with 1 family member having the typical features of albinism and reduced vision, while

another affected family member has no nystagmus and normal vision.[91,92] However, the presence of foveal hypoplasia, in addition to the excessive decussation detected by pattern offset-onset visual evoked potentials recorded from each occiput following monocular stimulation, seem to be the common features shared by these family members with variable expressivity of albinism. Moreover, the visual evoked potential can be used to differentiate patients with nystagmus due to albinism from patients with nystagmus due to hereditary or idiopathic congenital nystagmus.[159,169,170] Without the visual evoked potential, the diagnosis may be difficult to ascertain in the patient with albinism and minimal evidence of hypopigmentation, as the nystagmus waveforms are similar for albinism and congenital nystagmus. Visual evoked potentials have also been assessed in obligate carriers for albinism and have been found to be similar to normally pigmented controls.[170,171]

PRESENT STUDIES

While the various ocular features are essential to the diagnosis of either OCA or OA, it is clearly the limitation on visual acuity that is the most clinically significant for persons with albinism and of the most concern to the parents. The current investigation explores vision in albinism from 3 perspectives: Project I, the development of vision; Project II, the effect of light on measured visual acuity; and Project III, the relationship between melanin pigment in the macula and visual potential.

PROJECT I. VISUAL DEVELOPMENT IN ALBINISM

INTRODUCTION

Delayed visual maturation has been reported as both an isolated finding (group I), and in association with either mental retardation (group II) or ocular abnormalities (group III).[172-174] Reports of children with delayed visual maturation have occasionally included patients with albinism. These studies suggest that the rate of visual development may be delayed in albinism[120,121,174,175]; however, they include only a few patients with a diagnosis of albinism, and data are often grouped with patients who have different diagnoses. In addition, the assessment of vision is often qualitative. The patients' greater age at time of initial examination and reduced frequency of visual acuity determinations limit interpretation and generalized application to the rate of visual development in patients with albinism. Moreover, there has been no effort to relate visual development to the amount of ocular melanin pigment.

The acuity card procedure is a standard office technique to quantita-

tively assess visual acuity in young patients.[176-179] The cards present a rectangular gray field with a high-contrast, black-and-white striped patch of equal luminance located at one end of the card. Successive cards, presented with random location of the patch to the child's right or left, have progressively smaller stripes. Using preferential looking techniques, grating (resolution) acuity is measured by determining the highest spatial frequency that elicits a behavioral response from the child when observed by a masked examiner. This technique is part of the routine examination of children who are too young to cooperate with assessment of recognition acuity measured with letters, numbers, or figures. Statistically valid normative data for grating acuity, obtained from large populations of children with normal ophthalmologic examinations and normal development, are available to describe the development of both monocular and binocular grating acuity.[180,181] In contrast to previous studies, these more recent studies of normal children excluded individuals with larger refractive errors from the study population.

The current study examines data for grating acuity development in a group of young children with albinism, to determine how it differs from a normative population. In addition, the possible relationship of grating acuity to the amount of ocular pigment was investigated to determine if pigment production influenced acquisition of this visual function.

MATERIALS AND METHODS

Patients

This study was approved by the Review Board at this institution. After informed consent was received from the parents of the children, 40 consecutive patients under 3 years of age with a diagnosis of albinism were entered into a prospective study of visual development. Age at which vision was assessed was recorded as corrected age (ie, age from expected date of confinement [EDC]), for the 4 children who were born more than 2 weeks before EDC. No child in this study was born at a gestational age less than 36 weeks. Refractive correction was used with hyperopia greater than 4.50 diopters at 6 months of age and greater than 3.25 diopters at or beyond 1 year of age, myopia greater than 2.50 diopters at any age, astigmatism greater than 2.00 diopters at or beyond 2 years of age, and anisometropia greater than 2.50 diopters spherical equivalent, as determined by cycloplegic retinoscopy. The one exception was a patient who was found to have increasing astigmatism to the level of 3.00 diopters at 18 months of age. Owing to a marked head turn to dampen his nystagmus, refractive correction was not used, as eccentric viewing through the lens would distort the visual image.

A diagnosis of albinism was made by the ophthalmic features of absent or reduced pigment in the posterior iris epithelium, detected by transillumination with biomicroscopy, and absent or reduced melanin pigment in the fundus, in addition to foveal hypoplasia. All but 1 patient developed nystagmus. One patient underwent retroequatorial placement of all 4 horizontal rectus muscles at 15 months of age and another underwent a Kestenbaum-Anderson procedure for a 35° left head turn at 38 months of age. Nine patients were found to have amblyopia, determined by absence of maintained fixation using an accommodative target,[182-184] and received part-time occlusion therapy appropriate for age. Owing to technical difficulty in accurately performing visual evoked potentials to detect excessive crossing of the retinostriate fibers in very young children with albinism, only 2 of the patients underwent this confirmatory evaluation. Examination by a geneticist confirmed reduced cutaneous and hair pigment in 35 patients. Six of these patients had absent cutaneous, hair, and ocular pigment and were recorded as having OCA1A. Four additional patients with residual enzyme activity had a diagnosis of tyrosinase-related albinism (OCA1) based on molecular studies. For the remainder, type of albinism was determined by the geneticist after reviewing the clinical, biochemical, and molecular findings.[12]

Eye Examination

Eye examination included recording of iris transillumination using slit-lamp biomicroscopy in a darkened room, according to a previously published grading scheme.[37] In this scoring system, grade 1 transillumination represents scattered punctate transillumination defects, and grade 4 transillumination is full iris transillumination due to absence of melanin pigment. Macular development was assessed by indirect ophthalmoscopy through dilated pupils. Determination of the presence of melanin pigment in the macula and grading of macular transparency was done by examination with the direct ophthalmoscope, according to a standard set of reference photographs where grade 1 macular translucency represents choroidal vessels being easily detected in the macula, and grade 3 represents an opaque-appearing macula where the choroidal vessels cannot be visualized.[37]

Visual Acuity Procedures

The acuity card procedure, using the Teller acuity cards (Vistech Consultants, Inc, Dayton, Ohio), was used to determine visual acuity during the first 3 years of life in this project. Objective measurement of visual acuity was assessed by a certified technologist or orthoptist who had

extensive experience in examining young children and in performing the acuity card procedure. Using the method described by McDonald[176] and a full set of 15 acuity cards in one-half octave* steps from 0.32 to 38 cycles/cm, the tester was masked to the location of the 15.5 x 15.5-cm striped patch, and proceeded to a patch with smaller stripes until the location of the stimulus could not be detected by the child's behavioral response. Recognition of the grated patch required that the examiner observe head and/or eye movements toward one side of the card. At least three reversals were presented for each test condition, to assure an accurate judgment of recognition. The specific card with the highest spatial frequency (finest grating) at which the child could reliably localize the target at a defined distance was recorded in cycles per centimeter as the visual acuity. Patients were allowed to use compensatory head postures during the acuity measurements. Measurements were made without the use of a gray masking screen, at a distance of 38 cm from the child up to 12 months of age, 55 cm for children beyond 12 months but less than 34 months of age, and 84 cm for children 34 months of age and older. The Teller acuity cards were presented in a standard horizontal manner (vertical gratings) from lower to higher spatial frequencies, initially in one-octave steps until no response was elicited, and then in one-half octave steps, to determine threshold acuity, using a modified staircase procedure. The cards were first presented binocularly, and then monocularly, with the right eye tested first, under standard luminance of greater than 10 candela/m^2. An occlusive patch was used for monocular acuity measurement, because fogging the nontested eye was not feasible in this young group of patients with nystagmus and head turns. The measurements were compared with previously published normative data.[180,181]

For children reaching an age of greater than 3 years during the study, binocular and monocular recognition acuities were also recorded using picture matching (linear Allen figures), letter matching (HOTV test), or letter identification (Snellen acuity), with a letter acuity being preferred if the child could cooperate with the testing. Testing was performed at 20 ft, using the BVAT II (Mentor Ophthalmics, Santa Barbara, Calif) and refractive correction. The line with the smallest letters of which the child could successfully identify at least half of the symbols was recorded as recognition acuity. The caretakers had received information on practicing the technique of matching pictures or letters, or identifying letters, prior to the visit.

*An octave is a doubling or halving of the visual acuity (eg, the difference between 2.20 cycles/degree and 4.40 cycles/degree, or the difference between a Snellen acuity of 20/50 and 20/100. At a test distance of 55 cm, grating acuity of 2.40 cycles/degree is approximately equivalent to Snellen acuity of 20/60.

Parental Assessment of Visual Development

An attempt was made to correlate the objective findings of the visual acuity measurements with the parents' subjective assessment of visual development. Parents were queried regarding their perception of their child's visual development by completion of a written questionnaire. They were also asked if imaging techniques were used to evaluate the child's vision or ocular characteristics prior to a diagnosis of albinism being made.

Data Analysis

Grating acuity was converted from cycles per centimeter to cycles per degree for analyses. For data analysis, grating acuity was converted to logarithmic values. No assumptions regarding distribution of the data were made, and therefore nonparametric tests were used for statistical evalution. The Wilcoxon matched pairs test was conducted for interocular acuity differences for monocular acuities in the following ten age groups: 1, 3, 6, 9, 12, 15, and 18 months (± 1 months), and 24, 30, and 36 months (± 2 months). Grating acuity measurements in these age-groups were compared with current normative data from Mayer and associates[180] for monocular acuity, and from Salomão and Ventura[181] for binocular acuity. A relationship between the presence or absence of pigment and grating acuity was evaluated using the Mann Whitney U test. Finally, Pearson's correlation coefficient was used to evaluate the relationship between grating acuity and recognition acuity, after both acuities had been expressed as cycles per degree on a logarithmic scale.[185,186] Statistical significance was defined as $P < .05$. Data analyses were performed using STATISTICA (StatSoft, Tulsa, Okla).

RESULTS

Twenty-five males and 15 females under 3 years of age participated in this grating acuity study (Table I). The type of albinism was classified as ocular albinism in 5 patients, with 2 known to have X-linked OA. The remaining 35 patients had oculocutaneous albinism; included in this group were 9 patients with tyrosinase-related albinism, determined by absence of any pigment on clinical examination (OCA1A), or detection of a mutation of the tyrosinase gene; 1 patient with HPS; 1 patient with OCA1MP; and 1 patient with Brown OCA. For 22 additional patients with a pigmenting type of albinism, historical information and clinical examination suggested a diagnosis of OCA1 (9 patients) or OCA2 (13 patients). The type of albinism could not be determined in 1 patient.

Eye Examination

Ten of the patients had no ocular pigment detected, and slit-lamp biomicroscopy showed full iris transillumination (grade 4) (Fig 1). Thirty of the 40 patients developed some iris pigment: 8 had minimal iris pigment

TABLE I: VISUAL DEVELOPMENT STUDY: PATIENT CHARACTERISTICS IN PROJECT 1

PATIENT	SEX	TYPE OF ALBINISM	GRADE OF TRANS-IRIS ILLUMINATION	GRADE OF MACULAR TRANSLUCENCY	RECOGNITION VISUAL ACUITY*
1	M	OCA2	2	1	20/160 (S)
2	M	OCA1	1	2	20/125 (H)
3	M	OCA1A	4	2	20/125 (H)
4	M	OCA1A	4	1	20/125 (S)
5	F	OCA2	3	1	20/160 (H)
6	M	OA	3	2	NK
7	M	OA	3	2	NK
8	M	OCA1	2	2	NK
9	M	OCA1	0	2	20/100 (H)
10	F	OCA2	0	3	20/60 (H)
11	M	OCA2	3	1	20/125 (H)
12	M	OCA1A	4	2	NK
13	M	OCA2	2	2	NK
14	F	OCA1	1	3	20/60 (H)
15	F	OCA2	2	2	NK
16	F	OCA1	3	1	20/125 (S)
17	F	OCA2	4	1	NK
18	M	OCA1MP	2	3	20/200 (S)
19	F	OCA1	1	3	20/60 (S)
20	M	OA	2	1	20/70 (H)
21	M	OA1	2	3	20/100 (S)
22	F	OCA2	1	3	NK
23	M	OA1	3	2	NK
24	M	OCA1	1	1	20/125 (H)
25	M	OCA1	1	1	NK
26	M	Brown OCA	2	3	20/125 (S)
27	M	OCA2	4	2	NK
28	F	OCA1	4	2	20/200 (A)
29	M	OCA2	2	3	20/125 (H)
30	F	OCA1	1	3	20/80 (A)
31	F	OCA2	1	2	20/125 (S)
32	F	OCA1	2	2	20/160 (H)
33	F	OCA1	4	2	20/100 (S)
34	F	OCA2	1	3	20/70 (S)
35	M	HPS	3	2	20/100 (H)
36	F	OCA1A	4	2	20/160 (H)
37	M	OCA1A	3	2	20/100 (S)
38	M	OCA2	4	2	NK
39	M	NK	2	2	20/100 (A)
40	M	OCA1	4	1	NK

A, Allen figures; H, HOTV; S, Snellen letters; NK, not known.

*Best-corrected linear binocular recognition visual acuity. Baylor Video Acuity Tester (BVAT II) provides targets at both 20/125 and 20/160 levels. With previous methods of testing, vision in these patients would have been recorded at 20/200.

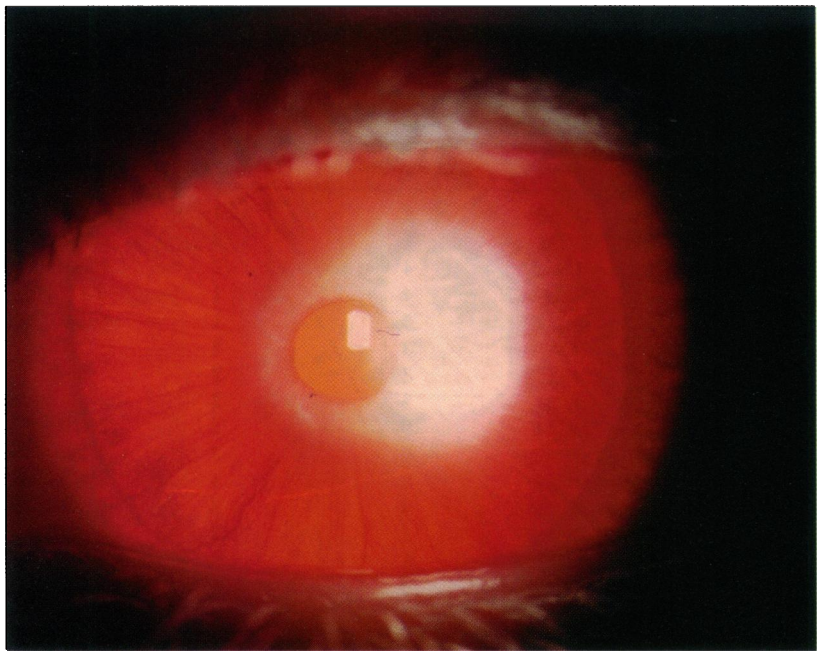

FIGURE 1
Slit-lamp photograph showing full iris transillumination (grade 4) due to complete absence of melanin pigment. Edge of lens is easily seen through translucent iris.

(grade 3 transillumination); 11 had moderate iris pigment (grade 2 iris transillumination); 9 had marked iris pigment (grade 1 iris transillumination) (Fig 2); and 2 had full iris pigment (no iris transillumination). Eight showed clinical evidence of fine, diffuse melanin pigment in the retinal pigment epithelium with direct ophthalmoscopy. Macular transparency was graded as 1 (choroidal vessels easily visible) in 10 patients, 2 (choroidal vessels visible but indistinct) in 20 patients, and 3 (choroidal vessels not visible in macula) in 10 patients. Pearson's correlation coefficient showed a statistically significant relationship between increasing iris grade (decreasing iris pigment) and decreasing grade of macular translucency (decreasing opaqueness) with r=-.406 (P = .009). No distinct relationship between either iris transillumination or macular transparency and type of albinism was found, but all patients with OCA1A had full iris transillumination, as expected.

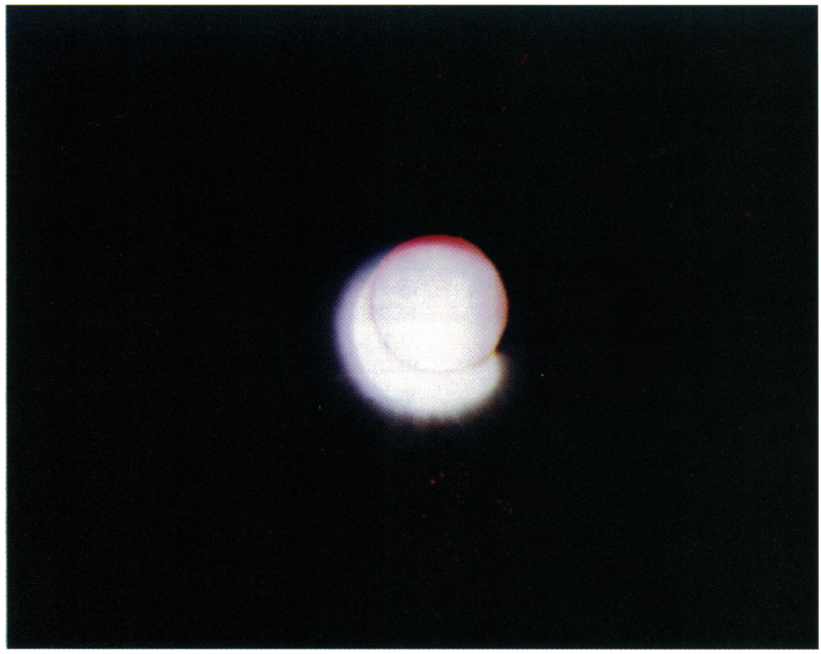

FIGURE 2
Slit-lamp photograph showing minimal iris transillumination (grade 1) due to presence of marked amount of melanin pigment in posterior iris epithelium.

Success in Testing

Binocular grating acuity measurements were successfully obtained in 86.8% of the test sessions, and monocular measurements were obtained in 83.6% of the sessions. Specific testability rates for each age-group are given in Table II. The number of independent visual acuity sessions to measure grating acuity was: one, 7 children; two, 7 children; three, 7 children; four or more, 19 children. Twenty-seven children participated in a recognition acuity measurement at age 3 years or older. Recognition acuity was measured with Snellen letters in 11 patients, with HOTV letters in 13 patients, and with Allen figures in 3 patients.

Development of Grating Acuity

Grating acuity (cycles per degree) was converted to octaves ($\log_{10}$ [cycles/degree] ÷ 0.301) for reporting of standard deviation and for plotting of data. Of 152 monocular grating acuity testings, there was an interocular acuity difference of one-half octave or less in 89% of testings and

TABLE II: SUCCESS IN GRATING ACUITY TESTING FOR PATIENTS WITH ALBINISM

AGE (MO)	BINOCULAR		MONOCULAR	
	No.	%	No.	%
1	2/2	100.0	1/2	50.0
3	6/9	66.7	3/9	33.3
6	15/18	83.3	12/18	66.7
9	14/15	93.3	15/15	100.0
12	22/26	84.6	24/26	92.3
15	9/13	69.2	10/13	76.9
18	12/14	85.7	12/14	85.7
24	20/22	90.91	20/22	90.9
30	19/19	100.0	16/19	84.2
36	13/14	92.9	14/14	100.0

one octave or less in 97%. In 86% of monocular testings, the same acuity was recorded for the right and left eyes. The difference between binocular and monocular grating acuity was significantly different at the following ages: 6 months ($P = .028$), 12 months ($P = .002$), 24 months ($P = .002$), and 30 months ($P = .008$), using the Wilcoxon matched pairs test.

Scatterplots of the raw data for monocular and binocular acuity measurements show high intersubject variability (Figs 3 through 5). The means and standard deviations for grating acuity data, adjusted to include only data that were distributed within the defined age-groups, are given in Tables III and IV. Comparison with age-matched norms[180,181] is shown in the accompanying graphs (Figs 6 and 7). Monocular data (Table III, Fig 6) is recorded only for right eyes, as right and left monocular acuity comparisons showed no statistically significant difference for any of the age-groups, and statistical methods are most valid for monocular data when information from only one eye is used.[187]

Mean binocular and monocular acuities for the study population are reduced approximately two to three octaves compared with available means for a normal population between 6 months and 3 years of age. Despite a reduced number of acuity measurements within the first 6 months of life, it appears that vision does not initially fail to develop and then plateau to a lower visual level than normal; rather, binocular and monocular vision at any age appear to be equal to or less than expected for normal. Only the binocular means at 1 and 3 months of age fall within the tolerance limits for 90% of the normal population with 95% probability. Only at 3 months of age does the monocular grating acuity fall within the lower 2.5% prediction limits of normal.

Statistical analysis was performed to detect a difference in grating acuity between patients without iris pigment (grade 4 iris transillumina-

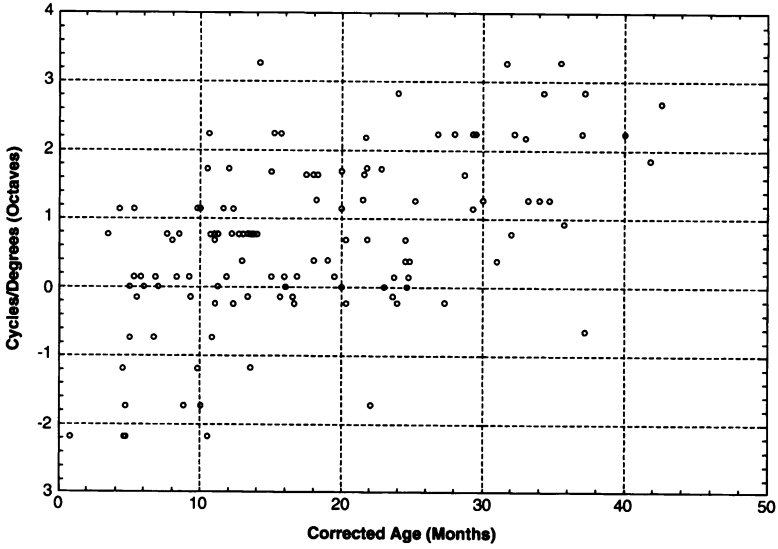

FIGURE 3
Scatterplot of raw data for monocular (right eye) grating acuity in patients with albinism. The y-axis is plotted in octaves.

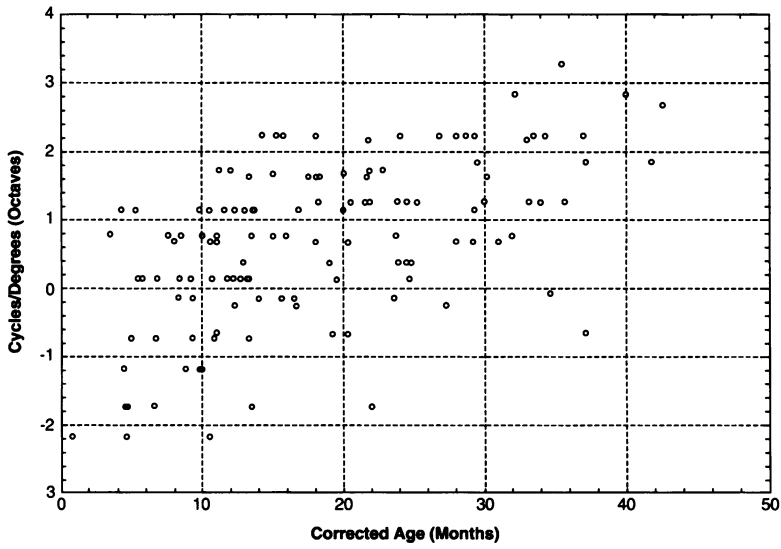

FIGURE 4
Scatterplot of raw data for monocular (left eye) grating acuity in patients with albinism. The y-axis is plotted in octaves.

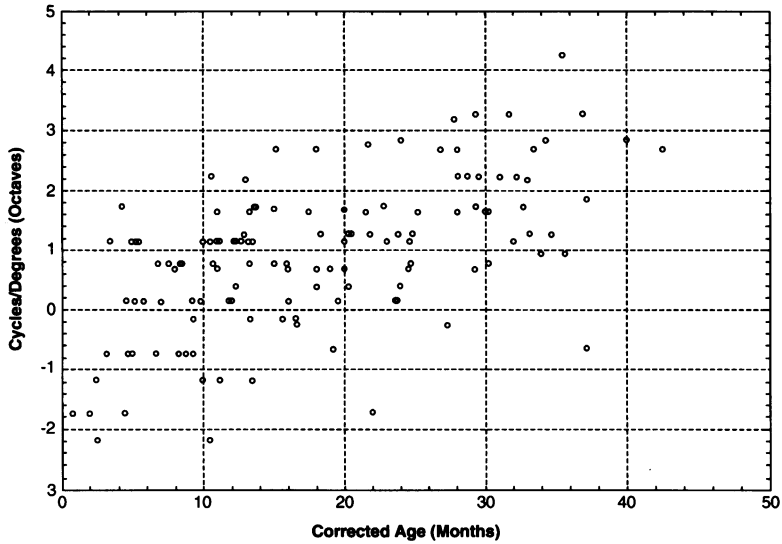

FIGURE 5
Scatterplot of raw data for binocular grating acuity in patients with albinism. The y-axis is plotted in octaves.

TABLE III: MONOCULAR GRATING ACUITY IN ALBINISM

AGE (MO)	N	MEAN ACUITY (CYCLES/DEGREE)	SD* (OCTAVES)
1	1	0.22	-
3	3	1.37	0.04
6	12	0.95	4.11
9	15	1.47	0.30
12	24	1.66	0.41
15	10	2.87	1.50
18	12	2.19	0.27
24	20	2.26	0.74
30	16	3.45	1.13
36	14	4.45	1.30

* SD, standard deviation.

TABLE IV: BINOCULAR GRATING ACUITY IN ALBINISM

AGE (MO)	N	MEAN ACUITY (CYCLES/DEGREE)	SD° (OCTAVES)
1	2	0.30	-
3	6	1.31	0.27
6	15	1.24	0.47
9	14	1.40	0.20
12	22	2.19	0.06
15	9	2.04	0.84
18	12	2.56	0.93
24	20	2.69	0.94
30	19	4.47	1.37
36	13	5.76	2.27

° SD, standard deviation.

tion) and those patients with iris pigment (grades 1, 2, or 3 iris transillumination). No statistically significant difference was found between patients without and with iris pigment in any of the age-groups.

Recognition Acuity

Binocular corrected recognition acuities for Project I are indicated in Fig 8. Mean binocular recognition acuity for this group is 20/111. Regression analysis failed to show a significant relationship between grating acuity at 12, 24, or 36 months and recognition acuity.

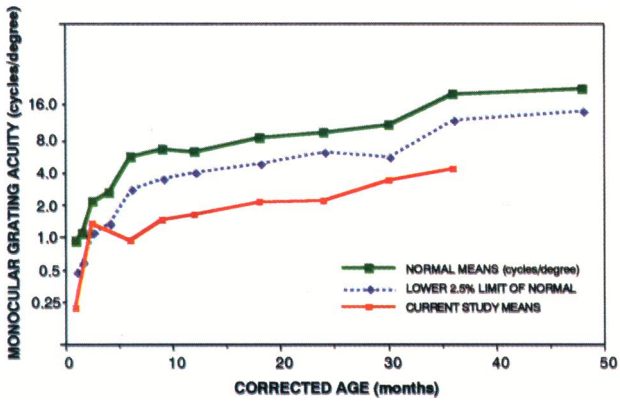

FIGURE 6

Monocular grating acuity development in patients with albinism, compared with means from normal population (Mayer et al[180]). Lower 2.5% limits for normal population are shown by dotted line.

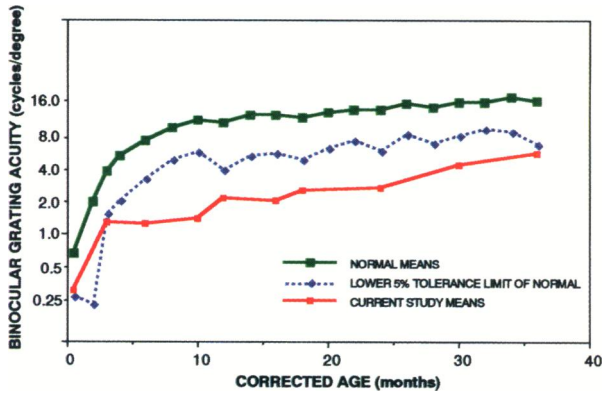

FIGURE 7

Binocular grating acuity development in patients with albinism, compared with means from a normal population (Salomão and Ventura[151]). Lower 5% tolerance limit for normal population is shown by dotted line.

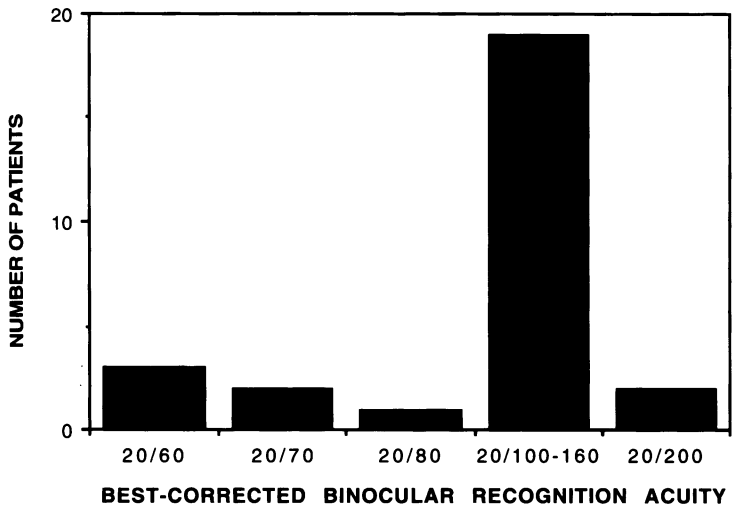

FIGURE 8

Distribution of recognition acuities in children with albinism in Project I (mean acuity, 20/111).

Parental Assessment

Parents of 33 children in this study returned the questionnaire regarding their child's visual development (response rate, 83%). One indicated that visual development was unknown, as the child was adopted at 22 months of age. Of the remaining 32 responses, 69% judged their child's visual development to be slow, recording a mean age of 5.4 months (range, birth to 18 months) at which the child began to visually respond in a manner similar to other children. Parents who did not feel their child showed delayed visual development reported a mean age of 2.5 months (range, birth to 3 months) at which visual responsiveness was similar to that of a child with normal vision. Parents of children who had older siblings were more likely to report that their child's visual development was slow, but this difference was not statistically significant ($P > .05$, chi-square analysis). Six children had undergone normal cranial imaging studies for their delayed visual development and nystagmus prior to a diagnosis of albinism being made.

DISCUSSION

The acuity card procedure is a reliable and efficient method of assessing grating acuity with high success rates for testability in the preverbal child, the child with ocular or neurological disorders, and the child with developmental delay.[175-181,188-193] By observing a child's behavioral response, the examiner can detect the highest spatial frequency that the child can visually resolve. Vision as assessed with the acuity card procedure develops rapidly within the first 6 months of life and then more slowly progresses to nearly an adult level by approximately 3 years of age in a normal population.[180,181,194] This duration required for visual development has been attributed to progressive foveal development, optic nerve and tract myelination, and central nervous system maturation.[195-201] When delayed visual maturation occurs, it may occur as an isolated finding or be associated with neurologic or ocular abnormalities.[174] This study is the first to report grating acuity in a large group of children with albinism, and to compare these results with normative data for visual development from the first 3 years of life. The results suggest that albinism is one of the ocular disorders associated with abnormal visual maturation, in addition to reduced visual potential.

The visual potential in albinism is usually limited, presumably owing to the combination of foveal hypoplasia, nystagmus, photosensitivity, and other less well-recognized factors. Wilson and associates[96] have studied various psychophysical visual functions in 2 children with albinism and concluded that the deficits in spatial vision may be due to an arrest in reti-

nal development. Fielder and colleagues[89] described the abnormal visual development in albinism as reduced or absent responsiveness at birth, with rapid improvement to a normal level thereafter coincident with the onset of nystagmus; this is followed by a plateau in visual development so that continued improvement to a normal level of acuity is not achieved. In another study, Fielder and colleagues[174] examined recovery of visual function by qualitative means in 6 patients with delayed visual maturation and nystagmus, 2 of whom had albinism. For this group, the range of visual improvement was between 16 and 36 weeks of age, and variability in time and speed of visual recovery was noted, with the maximal level of vision correlating with the ocular diagnosis accounting for the nystagmus. Jacobson and coworkers[88] studied development of grating acuity in an infant with tyrosinase-negative OCA, using forced-choice preferential looking techniques, with a luminance level of 13 cd/m^2. They found that acuity was similar to normal infants until about 15 months of age, when it began to progressively deteriorate until about 3 years of age. In contrast to the results of previous reports, the results of the current study suggest that the response to the grating of the acuity cards is reduced in the first 3 years of life in patients with albinism, although the rate of both monocular and binocular development tends to parallel the norm, particularly at ages greater than 6 months. Although limited data were available during the first 6 months of life, vision during this early time period may be closer to normal, suggesting an asymptotic curve of visual development in albinism, compared with a normal population.

In this study, observation by parents supports the concept of delayed visual development in albinism, particularly when parents have had the opportunity to observe visual development in a normally sighted older sibling. However, their responses were retrospective and required recollection of events that occurred months to years earlier. The variability of parental impressions of visual development of their children with delayed visual maturation, compared with measurement of visual function using grating acuity, has been noted previously.[121]

Witkop and associates[13] suggested that visual potential is related, in part, to the amount of ocular pigment. However, this study of young children did not show a significant relationship between ocular pigment production and visual development, as assessed by the acuity card procedure. This may be related to the smaller number of subjects in the nonpigmented group (10) compared with the pigmented group (30). In addition, patients with varying grades of pigment were grouped for data analysis, perhaps obscuring different rates of visual development for the various pigmenting types of albinism.

Both binocular and monocular grating acuity were assessed in this study and compared with data available from a normal population. Binocular acuity was better than monocular acuity in these patients with albinism. Binocular grating acuity has also been found to be one-half to one octave better than monocular acuity in normal patients.[181,202] With the increased amplitude of nystagmus than can occur with the opaque occlusion that was used in this study, one might expect that monocular acuity measurements would be more disparate when compared with normative data. Patients were allowed to use their compensatory head postures that could dampen the amplitude of the nystagmus and improve resolution of the grating,[117] as this provided the best estimate of their functional vision. The high rate of intersubject variability reported herein has also been noted in normal populations.[194] The interocular acuity difference noted in studies of normal children was similar to those reported here, perhaps because these children received refractive correction and were treated for amblyopia when it was detected. Although the majority of patients had three or more grating acuity determinations within the first 3 years of life, not all were available for testing at the same age intervals, introducing some bias into the data, and weighting it toward the patients who were able to return more frequently. It should be noted that only the data for the indicated age intervals were used for the visual development graphs, to allow comparison with published normative data that is based on a cross-sectional sample.

There are other inherent weaknesses in the present study. Although the number of children with albinism undergoing grating acuity measurements is greater than in other published studies, the number of acuity determinations in each age bin is limited compared with larger populations on which normative data were obtained. This reduced power of sample size limited the ability to detect a difference in the pigmented and nonpigmented groups. Owing to the small sample size during the first 6 months of life, when the rate of visual development is normally rapidly increasing, additional study during this time period is warranted. In addition, a slightly increased range of age for each group was used, with the potential for greater variability of data and reduced validity with comparison to normative data. Yet, the studies of both Mayer and associates[180] and Salomão and Ventura[181] used somewhat different age-groups of normal children and found similar results, suggesting that the modest increases in age ranges in the current study did not adversely affect comparisons.

Methodology for grating acuity measurements also varied from that described for normative data collection. A reduced distance to the grating was used at 9 and 12 months of age in the current study, compared with

the norms. Such a reduced distance has been recommended in testing patients with visual impairment.[203] Nonetheless, similar results have been recorded in larger studies of normal populations when test distance varied,[180,181] making it unlikely that the test distance influenced the outcomes. In addition, the start card varied in the current study, but such change in methodology has not been felt to significantly affect the accuracy of grating acuity measurement in a normative data study.[180] Lastly, test-retest variability was not evaluated, and interobserver reliability among the three testers was not measured, as recommended by Quinn and associates.[204] However, all testers in this study were similarly trained, had considerable experience in using the acuity card procedure, and had previously demonstrated agreement in measuring grating acuity in a clinical situation. Studies have shown good interobserver agreement when multiple examiners are used and training is similar.[180,181,205]

In this study, the cards were presented in the standard horizontal manner that orients the stripes vertically to allow direct comparison with normative data. This allows comparison of performance on a functional test of vision in children with albinism to that of a normal population, as is often requested by parents, educators, and visual consultants, realizing that grating acuity is not equivalent to measurement of Snellen acuity.[191,206] However, factors relating to grating orientation may have contributed to the reduced acuities measured in these patients with nystagmus due to albinism, compared with normative data for age. Since individuals with albinism typically have a predominantly horizontal component to their nystagmus, the vertical gratings may have been more difficult to resolve owing to blurring as the image moves across the retina.[96,207,208]

Such an increased sensitivity to horizontal stimuli has been previously reported when contrast sensitivity function was examined.[106] Meiusi and colleagues[209] found that grating acuity in adults with nystagmus due to either albinism or other disorders showed significantly improved acuity when the grating was oriented horizontally. However, in that study, improved monocular grating acuity of a magnitude greater than one octave was found in only 8 of 40 eyes in patients with albinism. Another preliminary study[210] reported that acuity improved in infants with horizontal nystagmus when gratings were oriented to yield a nonstandard horizontal grating pattern; for infants with coarse nystagmus, vertical presentation of the card was also a factor in improved acuity.

Yet, others have not been able to correlate the parameters of nystagmus in patients with idiopathic congenital nystagmus or albinism to visual acuity measured with horizontal or vertical gratings.[211] Wilson and coworkers[97] have suggested that vertically oriented stimuli may produce only

modest broadening of spatial frequencies in patients with albinism.

While orientation of the grating may play a role in the measurement of grating acuity in patients with nystagmus, the degree of effect is difficult to ascertain and may vary among subjects, depending on the characteristics of their nystagmus waveforms. Furthermore, horizontal nystagmus can theoretically produce meridional amblyopia for orthogonal gratings[96,113] and thereby potentially influence grating acuity measurements.

Fixation behavior in individuals with horizontal nystagmus can be more difficult to judge when the card is presented horizontally, particularly when the amplitude of the nystagmus is coarse or the examiner is inexperienced. For this reason, nonstandard vertical presentation of the acuity cards may facilitate recognition of a preference for viewing one end of the gray card.[203] Despite the standard methods of presentation of the acuity cards in this study, the consistency of the data tend to support the concept of abnormal visual maturation in patients with albinism compared with a normal population. Future studies with larger groups of children with albinism may detect differences in acquisition of vision, as measured with grating acuity, for the different types of albinism. Certainly, prompt diagnosis of this congenital pigment abnormality and its associated abnormal rate of visual development can prevent expensive and unnecessary tests from being performed in this population, who typically have nystagmus, providing that other abnormal signs are absent.

Finally, this study failed to find a significant relationship between grating acuity and eventual Snellen acuity. Grating acuity, measured in cycles per degree, provides only an approximate estimate of the Snellen acuity. Overestimation of Snellen acuity and underrecognition of amblyopia have been previously reported.[212-214] In addition, the tendency of the acuity cards to overestimate recognition acuity has been previously reported in adult patients with albinism.[209] Similar findings have been suggested for 4 children (4 to 12.2 years of age) with OCA who had both grating and recognition acuities measured.[215] Another study[216] included 8 patients with OCA in a group of 23 patients with foveal/macular anomalies and found that grating acuity was better than recognition acuity for this group, with the discrepancy becoming more marked as acuity decreased. The results reported in this study show a similar overestimation of eventual Snellen acuity by grating acuity measurements. This discrepancy may be related to the difference in the psychophysical tasks required for grating and recognition acuities, or the larger size of the grated patch compared with the Snellen symbol.[215] While measurement of grating acuity allows comparison to normative data in children who are too young to participate in measurement of recognition acuity, it should not be used to predict eventual vision.

PROJECT II. EFFECT OF LIGHT ON GRATING ACUITY

INTRODUCTION

The acuity card procedure has been used as a reliable and efficient method of recording visual acuity in both preverbal children and in nonverbal individuals, regardless of age.[175,177,178,188,189,193,205,217-219] To allow valid comparison to published norms, standard measurement requires diffuse, even, indirect luminance at a minimum of 10 candela/m^2, and a subject-to-acuity card distance of 38, 55, or 84 cm.

Individuals with albinism typically show photosensitivity, often averting their eyes from bright illumination to avoid glare and discomfort.[14] The functional effect of illumination on visual acuity is not apparent. This study of grating acuity was undertaken in cooperative adults with albinism to determine if a change in illumination affected grating acuity and to ascertain the relationship between grating acuity, assessed under two different lighting conditions, to standard Snellen acuity using the ETDRS charts. The Teller Acuity Cards (Vistech Consultants, Inc, Dayton, Ohio) and ETDRS charts were selected for grating and recognition acuity, respectively, since these methods of assessing vision have standardized lighting requirements.[220] In addition, the ETDRS charts are designed as logMAR charts, in which there are an identical number of letters present on each line and a consistent progression of size to provide a geometric change in size by a constant factor.[221-223] This geometric progression is also present in the acuity cards.

METHODS

Patients

Twenty adult subjects with a diagnosis of albinism (group I) were recruited for the study, in addition to comparison groups of 20 adults with nystagmus due to diagnoses other than albinism (group II) and 20 adults with a normal comprehensive ophthalmic examination (group III). In group I, 12 patients had secondary OCA due to HPS, 6 had primary OCA, and two had OA. Diagnoses for group II included congenital motor nystagmus (12 patients), optic atrophy (3 patients), retinopathy of prematurity (2 patients), nystagmus following encephalopathy (1 patient), aniridia (1 patient), and deprivation amblyopia due to congenital cataracts (1 patient). Approval for the study was obtained from the Institutional Review Board. Signed consent was obtained from all subjects after the nature of the testing had been fully explained. All were paid a small honorarium for their participation in the study.

Visual Acuity Procedures

For all visual acuity measurements, best refractive correction was used, determined by manifest refraction with refinement. Patients were allowed to used their desired head posture in order to measure their best vision. For monocular acuity testing, fogging with a +5.00-diopter lens over the untested eye was used to reduce the amplitude of the latent component of the nystagmus and avoid possible degradation of acuity.

Monocular acuity using the ETDRS charts was measured first. Binocular recognition acuity using the ETDRS charts was then recorded for group I. Vision with the ETDRS logMAR charts was recorded at 4 m, using room lighting as defined for the ETDRS study (actual mean illuminance of 65 foot-candles, measured with a Sekonic Exposure Meter, model L398).

Grating acuity was then assessed with the acuity card procedure without use of the gray masking screen. The full set of acuity cards ranging from 0.32 to 38 cycles/cm, in one-half octave steps, was used. Test distance was carefully maintained at 84 cm, and the cards were held in a vertical position (horizontal grating pattern) to reduce the potential for degradation of vertical stripes due to the predominately horizontal nature of nystagmus (Fig 9). Monocular grating acuity was recorded first, followed by binocular acuity, first for the right eye and then for the left eye. An examiner with considerable experience in acuity card testing administered the testing, and was masked to the location of the grated patch and the visual acuity recorded with the ETDRS charts. Since the subjects in this study were adults, they were asked to indicate the location of the grating when it could be visually resolved. Three reversals were presented for each test condition, and the highest spatial frequency at which the subject could repeatedly detect the grating was recorded in cycles per centimeter. Acuity card testing was first performed under standard illumination (mean illuminance, 37 foot-candles), as recommended in the Vistech manual. Subsequently, visual acuity was measured with increased indirect illumination provided by 2 lights on both sides of the cards, providing diffuse illumination measured at the test card at a mean of 88 foot-candles.

Data Analysis

Statistical analysis with nonparametric tests was performed to determine interocular acuity difference with monocular acuity testing under the 3 conditions (condition A, ETDRS vision; condition B, acuity card vision with standard illumination; condition C, acuity card vision with increased illumination). The differences in acuity for a particular group, under the 3 conditions, were evaluated using the Wilcoxon matched pairs test. For this

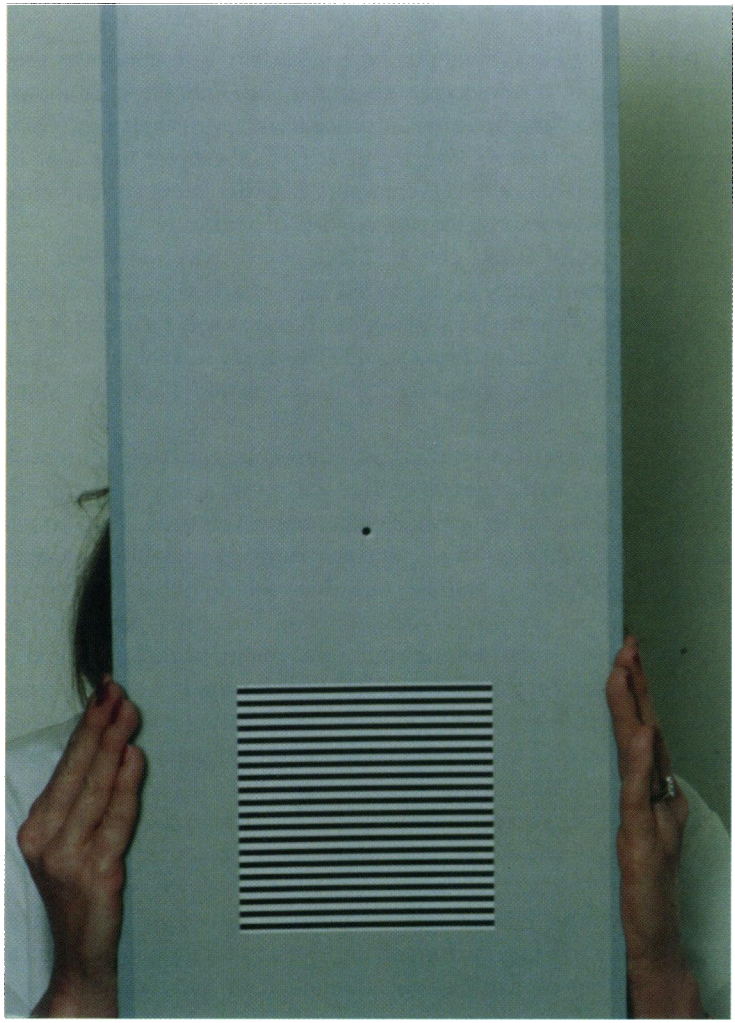

FIGURE 9
With vertical presentation of acuity cards, black-and-white grating that is located on one end of grey rectangular card is composed of horizontal stripes.

comparison, both recognition and grating acuities were converted to $\log_{10}$ cycles/degree, using the convention of recognition acuity of 20/20 being equivalent to 30 cycles/degree.[185,186,196] In addition, comparisons between binocular and monocular acuity for the 3 groups were analyzed by Pearson's correlation coefficient.

RESULTS

Interocular Acuity Measurements

Interocular differences in monocular acuity measurements were not significantly different for the 3 test conditions (Table V). Thus, additional statistical analysis used only acuity from the right eye for monocular comparisons to avoid errors in analysis when both eyes from 1 subject are used.[187]

Grating Acuity Under Different Levels of Illumination

For patients with albinism (group I), the difference between either binocular or monocular grating acuity under standard illumination (condition B) and increased illumination (condition C) was statistically significant ($P < .05$), with better grating acuity being recorded under the condition of increased illumination (Table VI). Patients with nystagmus that was not due to albinism (group II) also showed a statistically significant improvement in both monocular and binocular grating acuity under the condition of improved illumination. The difference in grating acuity with increased illumination that was seen in groups I and II was not statistically significant in the group of patients with a normal ophthalmic examination (group III).

TABLE V: INTEROCULAR DIFFERENCES (*P* VALUES*) WITH MONOCULAR ACUITY TESTING

	CONDITIONS†		
	A	B	C
Group I	.191	.969	.097
Group II	.972	.834	.554
Group III	.508	.735	.109

* Wilcoxon matched pairs test.

† Condition A represents ETDRS charts, condition B represents acuity cards under standard illumination, condition C represents acuity cards under increased illumination.

Comparison of Grating Acuity and Recognition Acuity

For all groups, the distributions are shifted toward better monocular grating acuity measured under standard illumination than recognition acuity, although this was statistically significant only for the group of patients with albinism ($P < .001$). The mean difference between monocular recognition and grating acuities under standard illumination was .73 octave (SD = .95) for group I, .47 octave (SD = .84) for group II, and .02 octave (SD = .27) for group III. For all groups, there is a shift toward better monocular grating acuity under increased illumination compared with recognition acuity

TABLE VI: DIFFERENCES IN ACUITY (*P* VALUES°) BY TEST CONDITION

	CONDITIONS†		
	A VS B	A VS C	B VS C
Group I			
Monocular	<.001	<.001	.025
Binocular	<.001	<.001	.012
Group II			
Monocular	NS	.007	.011
Binocular	NA	NA	.006
Group III			
Monocular	NS	.010	NS
Binocular	NA	NA	NS

NA, data not available; NS, not significant.
° Wilcoxon matched pairs test.
† Condition A represents ETDRS charts, condition B represents acuity cards under standard illumination, condition C represents acuity cards under increased illumination.

($P < .03$ for all groups). The mean difference between monocular recognition acuity and grating acuity under increased illumination was 1.19 octave (SD = .65) for group I, .75 octave (SD = .70) for group II, and .15 octave (SD = .24) for group III.

Comparison of Monocular and Binocular Acuities

Pearson's correlation coefficient for monocular versus binocular acuity in group I was strongly positive for each of the 3 test conditions, suggesting that reduction in acuity due to increased amplitude of nystagmus with fogging for monocular acuity testing was minimal (condition A: $r = .961$, $P < .001$; condition B: $r = .804$, $P < .001$; condition C: $r = .861$, $P = < .001$). A similar relationship between monocular and binocular grating acuity was noted for group II (condition B: $r = 790$, $P < .001$; condition C: $r = .897$, $P < .001$), but there was only a weakly positive correlation between monocular and binocular grating acuity for the normal control group (group III), and it was statistically significant only for the condition of increased illumination (condition B: $r = .305$, $P = .192$; condition C: $r = .453$, $P = .045$).

DISCUSSION

Filtering of ambient light by tinted spectacles or contact lenses or a cap or visor are often preferred by persons with albinism because of the associated photosensitivity that they frequently report.[102,109] One study[106] showed increased photosensitivity and associated discomfort when patients with tyrosinase-negative albinism were compared with patients with tyrosinase-

positive albinism. A study by Wilson and associates[96] indicated that photophobia could be eliminated by reduced luminance of 25 candela/m^2. Photosensitivity has been speculated to be related to the decreased filtering of light and increased light scattering due to reduced or absent ocular melanin pigment.[106] However, a direct relationship between subjective report of photosensitivity and amount of ocular pigment was not apparent in recently reported studies.[37,38]

It has also been suggested that reduction of the photosensitivity decreases nystagmus and improves visual function.[14] Edmunds[93] noted both improved vision and improved comfort in sunlight with scleral contact lenses that filtered light. In contrast, Silver[99] noted that some individuals with albinism did not prefer low illumination levels. While increases in ambient light may produce an adverse subjective response, this study is, to the author's knowledge, the first to determine the effect of increased illumination on grating acuity in a larger group of patients with albinism. The data in Project II show that increased illumination results in measurement of better grating acuity.

Teller and colleagues[224] used a mean luminance of either -0.5 or +0.7 log foot-lamberts in assessing grating acuity in a small number of normal infants between ages 1 and 6 months. Acuity values were slightly higher at the increased luminance levels but methodology varied at the different testing conditions. Dobson and coworkers[225] found that grating acuity measured with forced-choice preferential looking is reduced approximately one octave at -0.8 log cd/m^2, but is relatively unaffected by luminance levels above 1.0 log cd/m^2 (10 cd/m^2). Jacobson and associates[88] examined grating acuity under different luminance levels (34 cd/m^2 and 13 cd/m^2) in an adult and an infant, both of whom had tyrosinase-negative OCA. The infant showed reduced grating acuity with increased luminance and was obviously photophobic, whereas grating acuity in the adult was similar under the two levels of luminance. The results of the present study indicate that increased illumination does not adversely affect either monocular or binocular grating acuity in adult patients with either albinism or other conditions associated with nystagmus, and increased luminance may improve grating acuity. Anecdotal information presented by Fonda[102] also suggested that vision in albinism is not reduced when illumination is increased to 50 foot-lamberts (approximately 170 cd/m^2). Interestingly, grating acuity in the control group of normal patients in the current study was also better under the condition of increased illumination; this may be related to a spurious resolution of the interface between the grated patch and the gray background for gratings with the highest spatial frequencies when illumination is increased. [180,225]

The results of this study suggest that careful control of illumination according to standards is required for measurement of grating acuity that can be compared with normative values. While increased illumination may improve grating acuity, generalization to other visual settings is not possible because other factors, such as patient discomfort due to photosensitivity, may limit the practical application of increased illumination.

Other studies have shown that the acuity measured with the acuity card procedure in patients with low vision is often better than Snellen acuity measurements.[214,217] A similar relationship was noted in the groups with nystagmus that are presented herein. Thus, grating acuity is not equivalent to recognition acuity and should not be a substitute for the standard recording of a Snellen acuity when the later can be reliably measured .

PROJECT III. VISUAL POTENTIAL AND MELANIN PIGMENT

INTRODUCTION

In contrast to melanocytes in the iris stroma and choroid that migrate from the neural crest, melanocytes in the pigment epithelium of the iris and retinal pigment epithelium (RPE) originate from the neuroectoderm that lines the outer layer of the optic cup. In the embryonic eye, melanogenesis occurs differentially, with an increase in the number of melanosomes being located in the posterior RPE compared with the peripheral RPE.[227] With progressive development, the number of premelanosomes decreases while the number of mature melanosomes increases. In normal melanogenesis, melanin granules appear in melanosomes in the RPE from 7 weeks of embryologic development. Pigment develops in the posterior iris epithelium by 10 weeks of age.[228] By term, the pattern of ocular pigment in the human is mature, although the amount of melanin continues to increase. In addition, the yellow pigments within the sensory retina of the macula, lutein and zeaxanthin, seem to be present at birth and accumulate with ingestion of carotenoids.[229-231]

Along with progressive melanogenesis, modeling of the fovea occurs during normal embryogenesis. By 22 weeks' gestation, the site of the future fovea can be identified by the presence of a rod-free zone.[201] With development, the RPE cells in the macula become more uniformly tall and narrow. At birth, only a shallow foveal depression is present, with the structural anatomy of the human fovea not becoming mature until sometime between 15 and 45 months of age.[198,201] Concurrently, foveolar cone development occurs postnasally, reaching the adult stage of development by 45 months of age.[232] Isenberg[233] has identified 5 different stages of normal macular development, from an indistinct pigmented area (stage 1), to

the development of an annular reflex (stages 2 and 3), to the final development of a foveal pit (stage 4) and foveal light reflex (stage 5). In premature infants without retinopathy, Isenberg found that stage 5 occurred at a postconceptual age of 41.7 ± 4.0 weeks.

While individuals with all types of albinism have foveal hypoplasia, and it is not unusual to find some degree of melanin pigment in the iris, the fundus is often described as blond or amelanotic, suggesting that melanin pigment cannot be clinically detected. The purpose Project III is to describe a group of patients with albinism who were noted to have the appearance of melanin pigment present within the macula on ophthalmoscopic examination, and to relate this to iris pigment, visual acuity, and type of albinism, to determine if this clinical feature predicts visual function.

METHODS

Patients

The Institutional Review Board approved the study, and adult patients or guardians of children provided written consent. Between 1985 and 1994, 29 individuals out of approximately 165 patients with a diagnosis of albinism were identified with a coarsely granular pigment pattern in the macula using direct ophthalmoscopy, suggesting the presence of melanin pigment (Fig 10*). Patients whose amplitude of nystagmus or photosensitivity precluded accurate judgment of the presence of melanin pigment were not included. The grade of macular transparency[37] was noted, but a specific grade was not required for inclusion. Diagnosis of albinism was made on the basis of the ocular features of nystagmus, iris transillumination, foveal hypoplasia, and nonocular examination showing hypopigmentation in skin and hair. Eight patients also had visual evoked potentials performed, demonstrating the excessive decussation of the retinostriate fibers that is characteristic of albinism (Fig 11). In addition, 7 patients had mutations for the tyrosinase gene identified by molecular analysis.

Visual Acuity Procedures

Best-corrected binocular vision in these patients was recorded by recognition acuity using Snellen charts, the HOTV matching chart, or linear Allen figures, allowing the patients to use a compensatory head posture to dampen their nystagmus. The acuity card procedure was used to record vision in patients who were too young to participate in recognition acuity tasks. The true geometric visual acuity was used for statistical analysis[185,186]

*Identification of a granular pigment pattern can be difficult in fundus photographs, compared with direct ophthalmoloscopy, because the field is less magnified with the former, and high-quality fundus photographs can be difficult to obtain in patients with nystagmus.

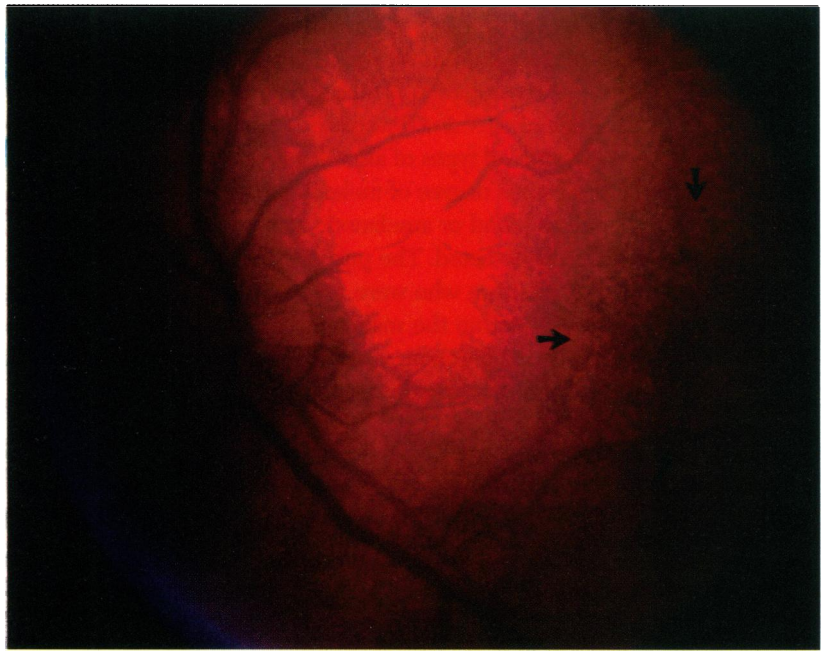

FIGURE 10A
Moderate amount of melanin pigment in macula of patient with OCA who had misrouting of optic fibers detected with visual evoked potentials. Examination of fundus photograph shows foveal hypoplasia and grade 3 macular translucency. Arrows indicate area examined with direct ophthalmoscopy to detect granular pigment pattern.

Eye Examination

Biomicroscopic examination of iris transillumination and direct ophthalmoscopy of the macula were used to quantitate ocular translucency.[37] The binocular indirect ophthalmoscope was used to assess the development of an annular reflex in the macula. A relationship between vision, iris transillumination, macular transparency, and type of albinism was sought, to further understand this subgroup of patients with albinism who had melanin pigment identified in their macula on clinical examination.

RESULTS

Table VII presents the clinical data for these 29 patients, ranging in age from 1 year to 49 years, with melanin pigment in the macula. Six of these had a diagnosis of OCA1, confirmed with molecular studies; an additional 6 were thought to have OCA1 on the basis of the history and clinical examination results; 1 of these had OCA1MP. Five patients had OCA2 and 3 had a diagnosis of Brown OCA based on history and examination results. Nine had a diagnosis of OA.

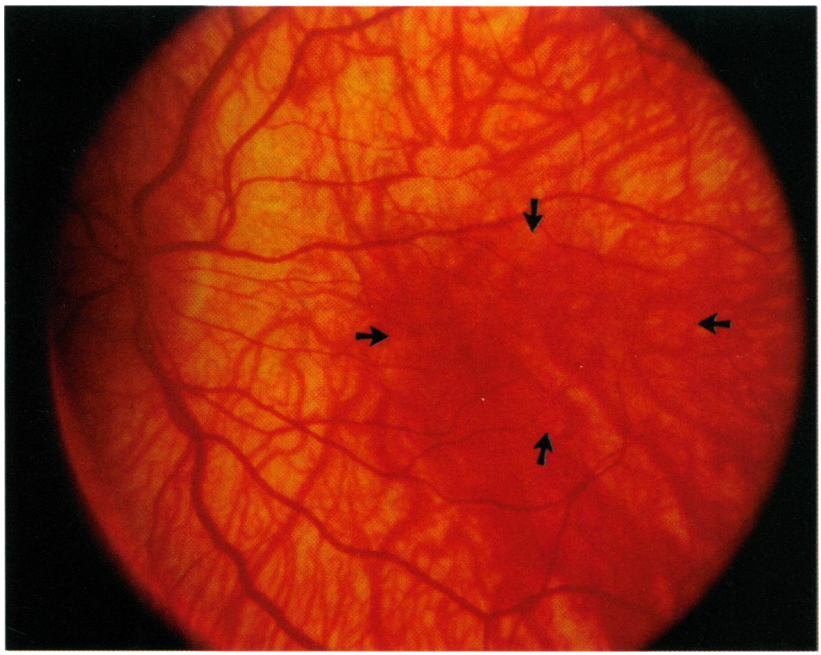

FIGURE 10B

Mild amount of melanin pigment in macula of patient with OCA1, who was found to have mutations in tyrosinase gene with molecular analysis. Arrows indicate area where granular melanin pigment could be detected with direct ophthalmoscopy. Abnormal wreathing of macular vessels and grade 2 macular translucency are noted.

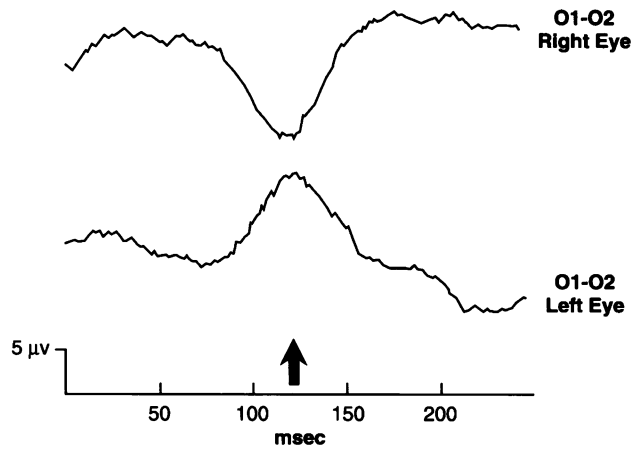

FIGURE 11

In contrast to normally pigmented individuals, patients with albinism show significant change (arrow) in difference potential (recorded from occipital scalp between locations O1 and O2) with monocular pattern onset/offset visual evoked potentials.

TABLE VII: CHARACTERISTICS OF PATIENTS WITH ALBINISM AND CLINICAL EVIDENCE OF MACULAR MELANIN (PROJECT III)

PATIENT	AGE (YR)	VISUAL ACUITY*	TYPE OF ALBINISM	GRADE OF IRIS TRANSILLUMINATION	GRADE OF MACULAR TRANSLUCENCY	ANNULAR MACULAR REFLEX	COMMENTS
1	4	20/80 (H)	OCA1†	1	2	+	VEP: misrouting
2	22	20/40	OA	1	3	-	VEP: misrouting; 3 yr after horizontal recti recession
3	18	20/50	OCA1	1	3	-	
4	6	20/60	OA	1	3	-	Stereo: 3000 sec
5	3	20/170 (T)	OCA1	2	2	+	Down syndrome
6	34	20/20	OCA1†	2	3	-	VEP: misrouting
7	4	20/25 (H)	OA3	0	3	-	Sibling of pt 8
8	13	20/50	OA3	1	3	-	VEP: misrouting
9	22	20/20	OCA2	1	2	-	VEP: misrouting; stereo: 100 sec; no nystagmus
10	12	20/50	OCA2	1	3	-	VEP: misrouting
11	5	20/70	OA3	1	3	+	
12	3	20/50 (H)	OCA1†	1	3	+	No nystagmus
13	28	20/80	OA3	3	3	-	Daughter of pt 26
14	6	20/60	OCA1†	1	3	-	VEP: misrouting
15	1	20/150 (T)	OCA2	0	3	-	
16	10	20/60	OCA1MP	1	2	-	6 mo after horizontal recti recession
17	26	20/60	OCA2	2	3	-	
18	5	20/100	Brown OCA	2	3	+	
19	8	20/80	OA3	1	3	-	
20	3	20/80 (A)	OCA1	1	3	-	
21	4	20/40 (H)	OCA1	1	2	-	
22	5	20/30	OCA1	1	3	-	Sibling of pt 22
23	10	20/25	OA3	0	2	+	Stereo: 100 sec

TABLE VII: CONTINUED

PATIENT	AGE (YR)	VISUAL ACUITY*	TYPE OF ALBINISM	GRADE OF IRIS TRANSILLUMINATION	GRADE OF MACULAR TRANSLUCENCY	ANNULAR MACULAR REFLEX	COMMENTS
24	10	20/30	OCA2	1	3	-	Stereo: 140 sec; VEP: misrouting
25	49	20/70	OA3	2	3	-	
26	14	20/40	OCA1†	2	2	-	
27	5	20/60 (H)	OCA1†	1	3	-	
28	5	20/50 (H)	Brown OCA	0	3	+	Sibling of pt 29; stereo: 100 sec
29	4	20/20 (A)	Brown OCA	0	3	+	Stereo: 100 sec; no nystagmus

A, Allen figures; H, HOTV; T, Teller acuity cards; VEP, visual evoked potential.

* Visual acuity: Best-corrected, binocular Snellen acuity, except as noted.
† Diagnosis made by molecular analysis.

Visual Acuity

All but 2 patients had best-corrected visual binocular visual acuity of at least 20/100 (Fig 12). A recognition acuity could not be recorded in these 2 patients. Twenty of the 29 patients had visual acuity of 20/60 or better, and 7 patients had vision better than 20/40. One patient with 20/40 vision had undergone recession of all 4 horizontal rectus muscles to dampen his nystagmus 3 years previously, and his preoperative vision was measured at 20/60+. Another patient also underwent 4 horizontal rectus muscle recession for nystagmus dampening; his visual acuity was 20/60 before and 6 months after the surgery. The mean binocular recognition acuity for patients included in this study was 20/47, which is significantly better than the mean visual acuity of 20/111 for the nonselected group of patients with albinism in Project I ($P < .001$). Stereoacuity was present in 6 patients in Project III, all of whom had visual acuity measured at 20/60 or better. In addition, nystagmus was not observed in 3 patients; 2 of these had visual acuity measured at 20/20, and vision was 20/50 in the third.

Eye Examination

All patients had granular brown-black pigment dispersed in the macula, but such granularity was not evident beyond the macula. All patients had foveal hypoplasia, with absence of a foveal light reflex. In 8 patients, an incompletely developed annular depression was detected in the macula with binocular indirect ophthalmoscopy, but the normal foveal architec-

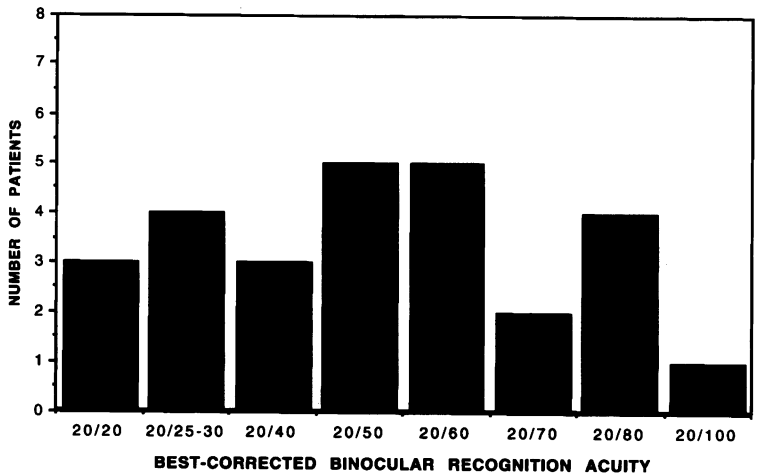

FIGURE 12

Distribution of binocular recognition acuities in patients with albinism and melanin pigment in their maculas (mean acuity, 20/47).

ture was not appreciated (Fig 13). In these patients, visual acuity ranged from 20/20 to 20/170.

Five patients showed no iris transillumination by slit-lamp biomicroscopy. Of the remaining 24 patients, 17 had grade 1 transillumination, 6 had grade 2 transillumination, and only 1 showed grade 3 transillumination. Macular translucency was recorded as grade 2 for 7 patients and grade 3 for 22 patients. There were no patients with grade 1 macular translucency. An annular reflex in the macula was found in patients with either grade 2 or grade 3 maculas.

Assuming that the data were not normally distributed, nonparametric tests were selected for statistical analyses. Multiple Pearson's correlation coefficient showed no significant relationship between grade of iris transillumination and grade of macular transparency. In addition, there was no significant correlation between macular grade and recognition visual acuity. However, a moderate correlation between increased iris pigment (lower grade of iris transillumination) and increased visual acuity was noted ($r = -.408$, $P = .035$). There was not a significant correlation between either iris or macular grade and type of albinism.

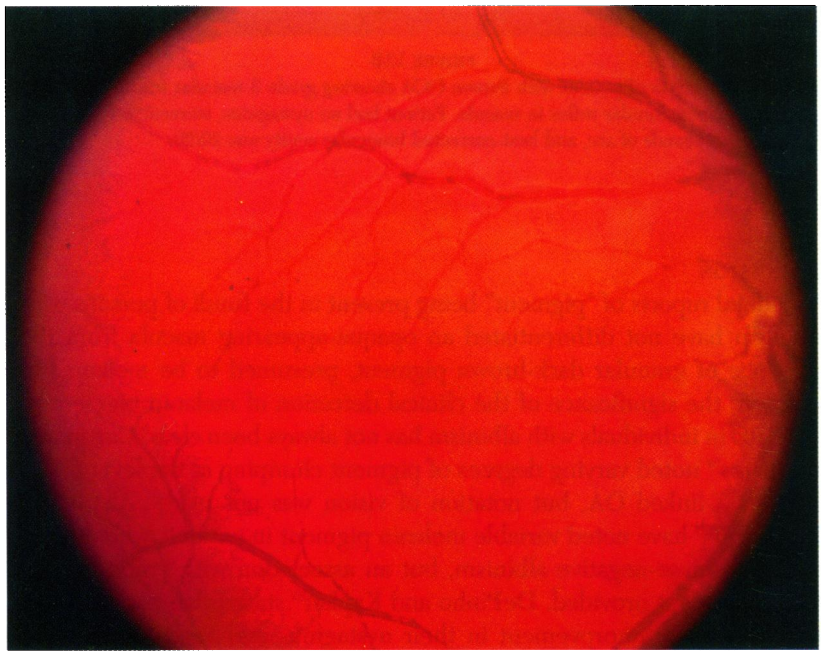

FIGURE 13A

Minimal development of annular reflex in macula is seen in this fundus photograph of patient with OA3. Patient had nystagmus, no stereovision, and best-corrected binocular visual acuity of 20/70.

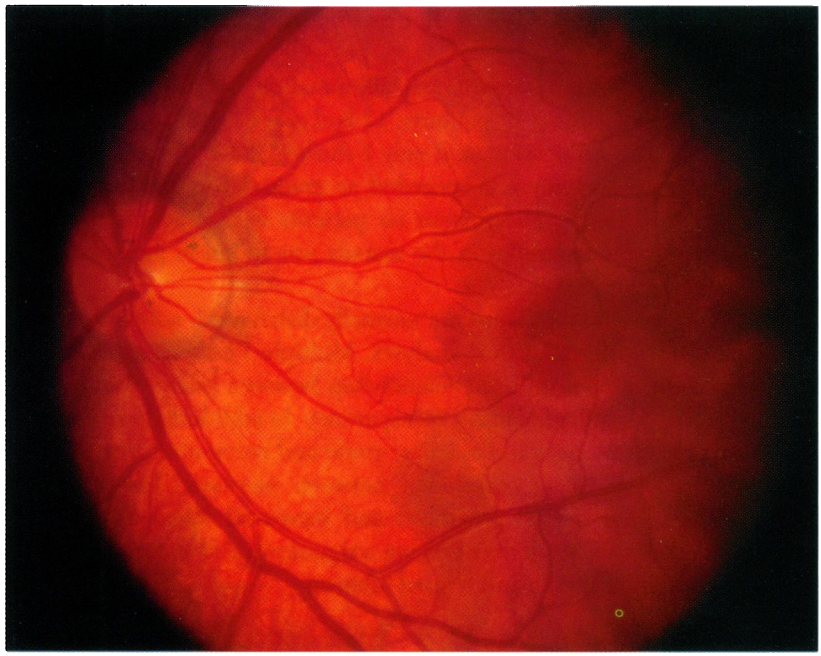

FIGURE 13B
Fundus photograph of patient with Brown OCA showing grade 3 macular translucency and mildly developed annular reflex in macula. Patient had no nystagmus, stereoacuity was measured at 100 seconds of arc, and best-corrected binocular acuity was 20/20.

DISCUSSION

Anecdotal reports of "pigment" being present in the fundi of persons with albinism have not differentiated an opaque-appearing macula from the presence of granular dark-brown pigment, presumed to be melanin. In addition, the significance of the clinical detection of melanin pigment in the RPE in individuals with albinism has not always been clear. Cortin and associates[78] noted varying degrees of pigment clumping at the level of the RPE in X-linked OA, but notation of vision was not made. Abadi and Dickinson[133] have noted variable melanin pigment in patients who did not have tyrosinase-negative albinism, but an association with vision or nystagmus was not provided. DePinho and Kaplan[53] stated that patients with HPS may have improvement in their nystagmus and vision as pigment accumulates in their fundus.

There are reports of individuals with albinism who have some pigment detected with ophthalmoscopic examination of the fundus, and

review of the literature shows that these persons often have better vision than is typically seen in albinism. Bergsma and Kaiser-Kupfer[10] reported retinal pigmentary mottling, detected with ophthalmoscopy and fluorescein angiography in 3 patients with albinism who had visual acuity of 20/30. Walker and associates[83] described a patient with X-linked OA who had normal macular pigment and 20/60 vision. Fundus pigment was reportedly normal in the macula for 2 males with X-linked ocular albinism reported by Goodman and colleagues,[87] but 1 patient's vision was only 20/150 and the other's was 20/70. In a description of X-linked OA in blacks, O'Donnell and coworkers[73] noted a "pigmented" fundus and "tigroid" appearance, in addition to foveal hypoplasia; this was referred to as "ocular albinism cum pigmento." Seven of their 10 patients had vision of 20/80 or better, and varying degrees of foveal hypoplasia were reported. Charles and coinvestigators[44] reported on a series of 74 males with X-linked ocular albinism and found better visual acuity associated with pigmentation masking the choroidal vessels in the macula; none of their patients demonstrated stereopsis. A patient with X-linked OA reported by Falls[84] had melanin pigment in the fundus, and vision measured 20/20. Reporting on patients with Brown OCA, King and associates[31] noted melanin pigment in the fundus with vision as good as 20/60.

Of the patients reported herein, 3 had Brown OCA. In addition, other types of albinism associated with melanin pigment in the macula in the current study included tyrosinase-related albinism (OCA1) with residual enzyme function, OCA2, and OA3. Although one third of the patients in the series reported herein had a clinical diagnosis of OA, the possibility of a tyrosinase-related type of OCA exists, as a recent report[70] has shown that some patients who had previously carried a diagnosis of OA were found to have mutations of the tyrosinase gene. Clearly, identification of melanin pigment in the macula can occur in various types of albinism but would not be expected in OCA1A, where no melanin pigment is produced in the eye, skin, or hair.

In addition, melanin pigment in the macula can occur without an "opaque" macula as judged by grade of macular translucency. This grading system is not specific for melanin pigment in the macula, although a correlation between grade of macular transparency and vision has been recently reported.[38] The variable opaqueness in the normal macula may be due to yellow pigment, but yellow pigment is felt to be absent in individuals with albinism.[71,229,234] A study using monochromatic fundus photography with 470-nm illuminating wavelength showed no macular yellow pigment in 3 patients with albinism, although variability in the visibility of choroidal vessels in the macula was apparent.[133] The investigators also noted that patients with albinism do not perceive the entoptic phenome-

na noted with Haidanger's brushes, most likely due to the absence of macular yellow pigment. A recent study demonstrated no variation in macular pigment density across the central retina in 7 patients with albinism.[235] The investigators suggest that this may be related to an inability of the retina in albinism to accumulate carotenoids, possibly owing to abnormal organization of macular photoreceptors and associated ganglion cells. Another possible explanation for the variable opaqueness of the macula is the presence of lipofuscin in the RPE.[236,237] Patients with albinism also have abnormal structure and distribution of photoreceptors in the macula,[1,71] and alteration in this arrangement could contribute to variable macular translucency. Clearly, variations in the opaqueness of the macula in individuals with albinism remains incompletely understood.

Vision in individuals with albinism is typically reduced to between 20/80 and 20/200.[14,61] The distribution of recognition acuities in Project I of the current study supports this level of reduced vision in an unselected group of patients with albinism. The results of Project III, from a selected group of patients with albinism and clinically detectable melanin pigment in the macula, suggest that this sign is associated with better visual acuity, compared with other typical patients reported with albinism. Furthermore, the presence of melanin pigment in the macula may be a clinical marker for other unusual ocular features in albinism, as 3 patients in this study had no observable nystagmus, 6 had evidence of stereoacuity, and 8 had an incompletely developed annular reflex in the macula. Other studies have also recognized the association between better vision and absence of nystagmus in individuals with albinism.[91,92] One explanation for these associations could be a variation in the number of misrouted fibers, perhaps related to a variable amount of pigment being present in the optic system during development. Future studies could be directed at RPE transplantation, genetic engineering, or other methods to foster the development of melanin pigment in the RPE in individuals with albinism, with the possibility of improving visual function. Finally, the presence of melanin pigment in the macula should not be a deterrent to the physician who is considering a diagnosis of albinism when examining a patient, particularly one with better vision than expected in albinism. The visual evoked potential to demonstrate the misrouting that is characteristic of albinism, as well as molecular studies to define the specific gene mutation, can be valuable in providing a specific diagnosis in these patients.

SUMMARY

This thesis addresses 3 different aspects of vision in albinism: visual development, effect of increased illuminance on grating acuity, and the visual

significance of detecting melanin pigment in the macula in patients with albinism.

Both monocular and binocular visual development, as measured with the acuity card procedure, seems to parallel the normal development of grating acuity at a level approximately 2 to 3 octaves lower than the means for a normal population from 6 months to 3 years of age. Although data in the first 6 months were limited, an asymptotic relationship between visual acuity in patients with albinism and normal individuals may more accurately describe the rate of acuity development in these patients. This study was unable to determine a relationship between development of grating acuity and the absence or presence of ocular pigment in patients with albinism. For patients maturing to a level where recognition acuity could be measured, mean acuity was reduced to 20/111. Grating acuity measured with the acuity card procedure overestimated eventual recognition acuity.

Increased illumination yielded improved grating acuity results in adults with albinism, despite the frequently noted symptom of photosensitivity in this disorder. The well-recognized overestimation of Snellen acuity by grating acuity measurements in low-vision patients was confirmed in this study of adults with albinism.

Finally, the importance of careful ophthalmoscopic examination of the macula to detect the granular appearance of melanin pigment is important to alert the clinician to the potential for better vision than is usually reported in albinism, in addition to the possible unexpected findings of stereoscopic vision and absence of nystagmus. Patients with melanin pigment in their maculas detected with direct ophthalmoloscopy showed a mean acuity of 20/47, which was significantly improved over the mean acuity of 20/111 in the first project, where an unselected group of patients with albinism had recognition acuity measured. This important observation has the potential for stimulating further research aimed at improving vision in albinism.

ACKNOWLEDGEMENTS

The author gratefully acknowledges the vision testing performed by Jane D. Lavoie, BA, CO, David A. Philiph, COMT and Susan S. Havertape, DBO, CO, and slit-lamp and fundus photography performed by William C. McMichael, COMT, CRA. Richard A. King, MD, PhD performed clinical genetics examinations and with the support of William S. Oetting, PhD and laboratory staff, conducted the molecular analyses for the patients reported herein. Wesley Obritsch provided assistance with the

statistical analyses. The author also wishes to thank Donna K. Knobloch for valuable technical expertise in preparing, assembling and reviewing the manuscript, Kathy McGill for technical assistance, Velma Dobson, PhD. for her consultation regarding the visual development study, and Alice J. Schmidt for her editorial assistance.

REFERENCES

1. Fulton AB, Albert DM, Craft JL. Human albinism: light and electron microscopy study. *Arch Ophthalmol* 1978; 96:305-310.
2. McCartney AC, Spalton DJ, Bull TB. Type IV melanosomes of the human albino iris. *Br J Ophthalmol* 1985; 69:537-541.
3. King RA, Hearing VJ, Creel DJ, et al. Albinism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *Metabolic and Molecular Basis of Inherited Disease.* New York, McGraw-Hill,1995, pp 4353-4392.
4. Witkop CJ, White JG, King RA. Oculocutaneous albinism. In: Nyham L, ed. *Heritable Disorders of Amino Acid Metabolism.* New York, Wiley, 1974, pp 177-261.
5. King RA, Witkop CJ Jr. Hairbulb tyrosinase activity in oculocutaneous albinism. *Nature* 1976; 263:69-71.
6. King RA, Witkop CJ. Detection of heterozygotes for tyrosinase-negative oculocutaneous albinism by hairbulb tyrosinase assay. *Am J Hum Genet* 1977; 29:164-168.
7. King RA, Olds DP, Witkop CJ. Characterization of human hairbulb tyrosinase: properties of normal and albino enzyme. *J Invest Dermatol* 1978; 71:136-139.
8. King RA, Olds DP. Hairbulb tyrosinsase activity in oculocutaneous albinism: suggestions for pathway control and block location. *Am J Med Genet* 1985; 20:49-55.
9. Kromberg JG, Castle DJ, Zwane EM, et al. Red or rufous albinism in southern Africa. *Ophthamic Paediatr Genet* 1990; 11:229-235.
10. Bergsma DR, Kaiser-Kupfer M. A new form of albinism. *Am J Ophthalmol* 1974; 77:837-844.
11. Fitzpatrick TB, Jimbow K, Donaldson DD. Dominant oculocutaneous albinism. *Br J Dermatol* 1974; 91(suppl 10):23.
12. King RA, Summers CG. Albinism. *Dermatol Clin* 1988; 6:217-228.
13. Witkop CJ Jr, Hill CW, Desnick S. Ophthalmologic, biochemical, platelet and ultrastructural defects in the various types of oculocutaneous albinism. *J Invest Dermatol* 1973; 60:443-456.
14. Abadi R, Pascal E. The recognition and management of albinism. *Ophthalmic Physiol Opt* 1989; 9:3-15.
15. Spritz RA, Strunk KM, Giebel LB, et al. Detection of mutations in the tyrosinase gene in a patient with type 1A oculocutaneous albinism. *N Engl J Med* 1990; 322:1724-1728.
16. Oetting WS, Mentink MM, Summers CG, et al. Three different frameshift mutations of the tyrosinase gene in type 1A oculocutaneous albinism. *Am J Hum Genet* 1991; 49:199-206.
17. Oetting WS, King RA. Molecular analysis of type 1-A (tyrosinase negative) oculocutaneous albinism. *Hum Genet* 1992; 90:258-262.
18. Shibahara S. Mutations of the tyrosinase gene in oculocutaneous albinism. *Pigment Cell Res* 1992; 5:279-283.
19. Park KC. Chintamaneni CD, Halaban R, et al. Molecular analyses of a tyrosinase-negative albino family. *Am J Hum Genet* 1993; 52:406-413.
20. Oetting WS, King RA. Molecular basis of type I (tyrosinase-related) oculocutaneous albinism: mutations and polymorphisms of the human tyrosinase gene. *Hum Mutat*

1993; 2:1-6.
21. Hu F, Hanifin JM, Prescott GH, et al. Yellow mutant albinism: cytochemical, ultrastructural, and genetic characterization suggesting multiple allelism. *Am J Hum Genet* 1980; 32:387-395.
22. Giebel LB, Tripathi RK, Strunk KM, et al. Tyrosinase gene mutations associated with type 1 B ("yellow") oculocutaneous albinism. *Am J Hum Genet* 1991; 48:1159-1167.
23. King RA, Wirtschafter JD, Olds DP, et al. Minimal pigment: a new type of oculocutaneous albinism. *Clin Genet* 1986; 29:42-50.
24. Summers CG, King RA. Ophthalmic features of minimal pigment oculocutaneous albinism. *Ophthalmology* 1994; 101:906-914.
25. Iljin VN, Iljin NA. Temperature effects on the color of the Siamese cat. *J Hered* 1930; 21:309-318.
26. Giebel LB, Tripathi RK, King RA, et al. A tyrosinase gene missense mutation in temperature-sensitive type 1 oculocutaneous albinism. *J Clin Invest* 1991; 87:1119-1122.
27. King RA, Townsend D, Oetting W, et al. Temperature-sensitive tyrosinase associated with peripheral pigmentation in oculocutaneous albinism. *J Clin Invest* 1991; 87:1046-1053.
28. Witkop CJ Jr, Nance WE, Rawls RF, et al. Autosomal recessive oculocutaneous albinism in man: evidence for genetic heterogeneity. *Am J Hum Genet* 1970; 22:55-74.
29. King RA, Creel D, Cervenka J, et al. Albinism in Nigeria with delineation of new recessive oculocutaneous type. *Clin Genet* 1980; 17:259-270.
30. King RA, Rich SS. Segregation analysis of brown oculocutaneous albinism. *Clin Genet* 1986; 29:496-501.
31. King RA, Lewis RA, Townsend D, et al. Brown oculocutaneous albinism: clinical, ophthalmological, and biochemical characterization. *Ophthalmology* 1985; 92:1496-1505.
32. Spencer WH, Hogan MJ. Ocular manifestations of Chédiak-Higashi syndrome: Report of a case with histopathologic examination of ocular tissues. *Am J Ophthalmol* 1960; 50:1197-1203.
33. Taylor WO. Albinos who bleed (Hermansky-Pudlak syndrome): the gypsy's warning. *Trans Ophthalmol Soc U K* 1981; 101:223-228.
34. Simon JW, Adams RJ, Calhoun JH, et al. Ophthalmic manifestations of the Hermansky-Pudlak syndrome (oculocutaneous albinism and hemorrhagic diathesis). *Am J Ophthalmol* 1982; 93:71-77.
35. Palmer DJ, Miller MT, Rao S. Hermansky-Pudlak oculocutaneous albinism: clinical and genetic observations of six patients. *Ophthalmic Paediatr Genet* 1983; 3:147-156.
36. Kinnear PE, Tuddenham EG. Albinism with haemorrhagic diathesis: Hermansky-Pudlak syndrome. *Br J Ophthalmol* 1985; 69:904-908.
37. Summers CG, Knobloch WH, Witkop CJ Jr, et al. Hermansky-Pudlak syndrome: ophthalmic findings. *Ophthalmology* 1988; 95:545-554.
38. Izquierdo NJ, Townsend W, Maumenee Hussels IE. Ocular findings in Hermansky-Pudlak syndrome. *Trans Am Ophthal Soc* 1995; 93:191-202.
39. Hales RH. Albinism with Axenfeld's syndrome. *Rocky Mount Med J* 1968; 65:51-52.
40. Benson W. Oculocutaneous albinism with Axenfeld's anomaly (Letter). *Am J Ophthalmol* 1981; 92:133-134.
41. Lubin JR. Oculocutaneous albinism associated with corneal mesodermal dysgenesis. *Am J Ophthalmol* 1981; 91:347-350.
42. Ricci B, Lacerra F. Oculocutaneous albinism and corneal mesodermal dysgenesis (Letter). *Am J Ophthalmol* 1981; 92:587.
43. van Dorp DB, Delleman JW, Loewer-Sieger DH. Oculocutaneous albinism and anterior chambre cleavage malformations: not a coincidence. *Clin Genet* 1984; 26:440-444.
44. Charles SJ, Green JS, Grant JW, et al. Clinical features of affected males with X linked ocular albinism. *Br J Ophthalmol* 1993; 77:222-227.

45. Witkop CJ, Babcock MN, Rao GH, et al. Albinism and Hermansky-Pudlak syndrome in Puerto Rico. *Bol Asoc Med P R* 1990; 82:333-339.
46. Hermansky F, Pudlak P. Albinism associated with hemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow: report of two cases with histochemical studies. *Blood* 1959; 14:162-169.
47. Hardisty RM, Mills DC, Ketsaard K. The platelet defect associated with albinism. *Br J Haematol* 1972; 23:679-692.
48. White JG, Witkop CJ. Effects of normal and aspirin platelets on defective secondary aggregation in Hermansky-Pudlak syndrome: a test for storage pool deficient platelets. *Am J Pathol* 1972; 68:57-66.
49. Davies BH, Tuddenham EG. Familial pulmonary fibrosis associated with oculocutaneous albinism and platelet function defect: a new syndrome. *Q J Med* 1976; 45:219-232.
50. Garay SM, Gardella JE, Fazzini EP, et al. Hermansky-Pudlak syndrome: pulmonary manifestations of a ceroid storage disorder. *Am J Med* 1979; 66:737-747.
51. Schinella RA, Greco MA, Cobert BL, et al. Hermansky-Pudlak syndrome with granulomatous colitis. *Ann Intern Med* 1980; 92:20-23.
52. White DA, Smith GJ, Cooper JA Jr, et al. Hermansky-Pudlak syndrome and interstitial lung disease: report of a case with lavage findings. *Am Rev Respir Dis* 1984; 130:138-141.
53. DePinho RA, Kaplan KL. The Hermansky-Pudlak syndrome: report of three cases and review of pathophysiology and management considerations. *Medicine* 1985; 64:192-202.
54. Witkop CJ, Krumwiede M, Sedano H, et al. Reliability of absent platelet dense bodies as a diagnostic criterion for Hermansky-Pudlak syndrome. *Am J Hematol* 1987; 26:305-311.
55. Mahadeo R, Markowitz J, Fisher S, et al. Hermansky-Pudlak syndrome with granulomatous colitis in children. *J Pediatr* 1991; 118:904-906.
56. Chédiak M. Nouvelle anomalie leucocytaire de caractére constitutionnel et familial. *Rev Hemat* 1952; 7:362-367.
57. Higashi O. Congenital gigantism of peroxidase granules: the first case ever reported of qualitative abnormality of peroxidase. *Tohoka J Exp Med* 1954; 59:315-332.
58. BenEzra D, Mengistu F, Cividalli G, et al. Chediak-Higashi syndrome: ocular findings. *J Pediatr Ophthalmol Strabismus* 1980; 17:68-74.
59. Windhorst DB, Zelickson AS, Good RA. Chediak-Higashi syndrome: hereditary gigantism of cytoplasmic organelles. *Science* 1966; 151:81-83.
60. Lockman LA, Kennedy WR, White JG. The Chediak-Higashi syndrome: electrophysiologic and electron microscopic observations on the peripheral neuropathy. *J Pediatr* 1967; 70:942-951.
61. Fonda G, Thomas H, Gore GV III. Educational and vocational placement, and low-vision corrections in albinism: a report based on 253 patients. *Sight Sav Rev* 1971; 41:29-36.
62. Nettleship E. On some hereditary diseases of the eye. *Trans Ophthalmol Soc U K* 1909; 29:57-198.
63. Scialfa AC. Ocular albinism in a female. *Am J Ophthalmol* 1972; 73:943-948.
64. O'Donnell FE Jr, King RA, Green WR, et al. Autosomal recessively inherited ocular albinism: a new form of ocular albinism affecting females as severely as males. *Arch Ophthalmol* 1978; 96:1621-1625.
65. Bergen AA, Samanns C, Schuurman EJ, et al: Multipoint linkage analysis in X-linked ocular albinism of the Nettleship-Falls type. *Hum Genet* 1991; 88:162-166.
66. Schnur RE, Nussbaum RL, Anson-Cartwright L, et al. Linkage analysis in X-linked ocular albinism. *Genomics* 1991; 9:605-613.

67. Charles SJ, Green JS, Moore AT, et al. Genetic mapping of X-linked ocular albinism: linkage analysis in a large Newfoundland kindred. *Genomics* 1993; 16:259-261.
68. Rose NC, Menacker SJ, Schnur RE, et al. Ocular albinism in a male with del (6)(q13-q15): candidate region for autosomal recessive ocular albinism? *Am J Med Genet* 1992; 42:700-705.
69. van Dorp DB, Eriksson AW, Delleman JW, et al. Åland eye disease: no albino misrouting. *Clin Genet* 1985; 28:526-531.
70. Summers CG, Fryer JT, Oetting WS, et al. Tyrosinase mutations show that patients with ocular albinism have oculocutaneous albinism. *Ophthalmology* 1995; 102(suppl):174.
71. O'Donnell FE Jr, Hambrick GW Jr, Green WR, et al. X-linked ocular albinism. An oculocutaneous macromelanosomal disorder. *Arch Ophthalmol* 1976; 94:1883-1892.
72. Garner A, Jay BS. Macromelanosomes in X-linked ocular albinism. *Histopathology* 1980; 4:243-254.
73. O'Donnell FE Jr, Green WR, Fleischman JA, et al. X-linked ocular albinism in blacks: ocular albinism cum pigmento. *Arch Ophthalmol* 1978; 96:1189-1192.
74. Szymanski KA, Boughman JA, Nance WE, et al. Genetic studies of ocular albinism in a large Virginia kindred. *Ann Ophthalmol* 1984; 16:183-196.
75. Charles SJ, Moore AT, Grant JW, et al. Genetic counselling in X-linked ocular albinism: clinical features of the carrier state. *Eye* 1992; 6:75-79.
76. Zelickson AS, Windhorst DB, White JG, et al. The Chédiak-Higashi syndrome: formation of giant melanosomes and the basis of hypopigmentation. *J Invest Dermatol* 1967; 49:575-581.
77. White JG, Clawson CC. The Chédiak-Higashi syndrome: the nature of the giant neutrophil granules and their interactions with cytoplasm and foreign particulates. *Am J Pathol* 1980; 98:151-196.
78. Cortin P, Tremblay M, Lemagne JM. X-linked ocular albinism: relative value of skin biopsy, iris transillumination and funduscopy in identifying affected males and carriers. *Can J Ophthalmol* 1981; 16:121-123.
79. Ohrt V. Ocular albinism with changes typical of carriers. *Br J Ophthalmol* 1956; 40:721-729.
80. Waardenburg PJ, van den Bosch J. X-chromosomal ocular albinism in a Dutch family. *Ann Hum Genet* 1956; 21:101-122.
81. Johnson GJ, Gillan JG, Pearce WG. Ocular albinism in Newfoundland. *Can J Ophthalmol* 1971; 6:237-248.
82. Pearce WG, Johnson GJ, Gillan JG. Nystagmus in a female carrier of ocular albinism. *J Med Genet* 1971; 9:126-129.
83. Walker BA, Martyn LJ, Coffman T. X-linked ocular albinism. *Birth Defects* 1971; 7:200-202.
84. Falls HF. Sex-linked ocular albinism displaying typical fundus changes in the female heterozygote. *Am J Ophthalmol* 1951; 34:41-50.
85. Gillespie FD. Ocular albinism with report of a family with female carriers. *Arch Ophthalmol* 1961; 66:774-777.
86. Gillespie FD, Covelli B. Carriers of ocular albinism with and without ocular changes. *Arch Ophthalmol* 1963; 70:209-213.
87. Goodman G, Ripps H, Siegel IM. Sex-linked ocular disorders: trait expressivity in males and carrier females. *Arch Ophthalmol* 1965; 73:387-398.
88. Jacobson SG, Mohindra I, Held R, et al. Visual acuity development in tyrosinase negative oculocutaneous albinism. *Doc Ophthalmol* 1984; 56:337-344.
89. Fielder AR, Dobson V, Moseley MJ, et al. Preferential looking: clinical lessons. *Ophthalmic Paediatr Genet* 1992; 13:101-110.
90. Kinnear PE, Jay B, Witkop CJ Jr. Albinism. *Surv Ophthalmol* 1985; 30:75-101.

91. Castronuovo S, Simon JW, Kandel GL, et al. Variable expression of albinism within a single kindred. *Am J Ophthalmol* 1991; 111:419-426.
92. Summers CG, Creel D, Townsend D, et al. Variable expression of vision in sibs with albinism. *Am J Med Genet* 1991; 40:327-331.
93. Edmunds RT. Vision of albinos. *Arch Ophthalmol* 1949; 42:755-767.
94. Taylor WO. Visual disabilities of oculocutaneous albinism and their alleviation. *Trans Ophthalmol Soc U K* 1978; 98:423-445.
95. Abadi RV, Pascal E. Visual resolution limits in human albinism. *Vision Res* 1991; 31:1445-1447.
96. Wilson HR, Mets MB, Nagy SE, et al. Albino spatial vision as an instance of arrested visual development. *Vision Res* 1988; 28:979-990.
97. Wilson HR, Mets MB, Nagly SE, et al. Spatial frequency and orientation tuning of spatial visual mechanisms in human albinos. *Vision Res* 1988; 28:991-999.
98. Abadi RV, Pascal E. Incremental light detection thresholds across the central visual field of human albinos. *Invest Ophthalmol Vis Sci* 1993; 34:1683-1690.
99. Silver JH. Low vision aids in the management of visual handicap. *Br J Physiol Opt* 1976; 31:47-87.
100. Collins B, Silver J. Recent experiences in the management of visual impairment in albinism. *Ophthalmic Paediatr Genet* 1990; 11:225-228.
101. Jay B. What was the matter with Dr Spooner? *Br Med J* 1987; 295:942-943.
102. Fonda G. Characteristics and low-vision corrections in albinism: A report of 161 patients. *Arch Ophthalmol* 1962; 68:754-761.
103. Summers CG, Oetting WS, King RA. Diagnosis of oculocutaneous albinism with molecular analysis. *Am J Ophthalmol* 1996; 121:724-726.
104. Pickford RW, Taylor WO. Colour vision of two albinos. *Br J Ophthalmol* 1968; 52:640-641.
105. Lourence PE, Fishman GA, Anderson RJ. Color vision in albino subjects. *Doc Ophthalmol* 1983; 55:341-350.
106. Abadi RV, Dickinson CM, Pascal E, et al. Retinal image quality in albinos: a review. *Ophthalmic Paediatr Genet* 1990; 11:171-176.
107. Gelbart SS, Hoyt CS. Congenital nystagmus: a clinical perspective in infancy. *Graefes Arch Clin Exp Ophthalmol* 1988; 226:178-180.
108. Miller D, Farley VH, McLaughlin R, et al. A light-shielded spectacle for albino patients. *Ann Ophthalmol* 1972; 4:611-612.
109. Hoeft WW, Hughes MK. A comparative study of low-vision patients: their ocular disease and preference for one specific series of light transmission filters. *Am J Optom Physiol Opt* 1981; 58:841-845.
110. Margolis S, Siegel IM, Choy A, et al. Oculocutaneous albinism associated with Apert's syndrome. *Am J Ophthalmol* 1977; 84:830-839.
111. Holmes JM, Cronin CM. Duane syndrome associated with oculocutaneous albinism. *J Pediatr Ophthalmol Strabismus* 1991; 28:32-34.
112. Kushner BJ. Functional amblyopia associated with organic ocular disease. *Am J Ophthalmol* 1981; 91:39-45.
113. Abadi RV, King-Smith PE. Congenital nystagmus modifies orientational detection. *Vision Res* 1979; 19:1409-1411.
114. Wirtschafter JD, Denslow GT, Shine IB. Quantification of iris translucency in albinism. *Arch Ophthalmol* 1973; 90:274-277.
115. Collewijn H, Apkarian P, Spekreijse H. The oculomotor behaviour of human albinos. *Brain* 1985; 108:1-28.
116. Guyer DR, Lessell S. Periodic alternating nystagmus associated with albinism. *J Clin Neuroophthalmol* 1986; 6:82-85.
117. Hoyt CS. Neurovisual adaptations to subnormal vision in children. *Aust N Z J*

Ophthalmol 1987; 15:57-63.
118. Abadi RV, Pascal E, Whittle J, et al. Retinal fixation behavior in human albinos. *Optom Vis Sci* 1989; 66:276-280.
119. Abadi RV, Pascal E. Ocular motor behaviour of monozygotic twins with tyrosinase negative oculocutaneous albinism. *Br J Ophthalmol* 1994; 78:349-352.
120. Fielder AR, Evans NM. Is the geniculostriate system a prerequisite for nystagmus? *Eye* 1988; 2:628-635.
121. Tresidder J, Fielder AR, Nicholson J. Delayed visual maturation: ophthalmic and neuro-developmental aspects. *Dev Med Child Neurol* 1990; 32:872-881.
122. Apkarian P, Eckhardt PG, van Schooneveld MJ. Detection of optic pathway misrouting in the human albino neonate. *Neuropediatrics* 1991; 22:211-215.
123. Krill AE. Total color blindness and albinism: two causes of subnormal visual acuity in children. *Postgrad Med* 1965; 37:279-283.
124. Cheong PY, King RA, Bateman JB. Oculocutaneous albinism: variable expressivity of nystagmus in a sibship. *J Pediatr Ophthalmol Strabismus* 1992; 29:185-188.
125. Anderson JR. Causes and treatment of congenital eccentric nystagmus. *Br J Ophthalmol* 1953; 37:267-281.
126. Kestenbaum A. Nouvelle operation de nystagmus. *Bull Soc Ophthalmol Fr* 1953; 6:599-602.
127. Dell'Osso LF, Flynn TJ. Congenital nystagmus surgery: a quantitative evaluation of the effects. *Arch Ophthalmol* 1979; 97:462-469.
128. Flynn JT, Dell'Osso LF. The effects of congenital nystagmus surgery. *Ophthalmology* 1979; 86:1414-1425.
129. Zubcov AA, Stärk N, Weber A, et al. Improvement of visual acuity after surgery for nystagmus. *Ophthalmology* 1993; 100:1488-1497.
130. Helveston EM, Ellis FD, Plager DA. Large recession of the horizontal recti for treatment of nystagmus. *Ophthalmology* 1991; 98:1302-1305.
131. von Noorden GK, Sprunger DT. Large rectus muscle recessions for the treatment of congenital nystagmus. *Arch Ophthalmol* 1991; 109:221-224.
132. Egbert JE, Anderson JH, Summers CG. Increased duration of low retinal slip velocities following retroequatorial placement of horizontal recti. *J Pediatr Ophthalmol Strabismus* 1995; 32:359-363.
133. Abadi RV, Dickinson CM. Monochromatic fundus photography of human albinos. *Arch Ophthalmol* 1983; 101:1706-1711.
134. Falls HF, Wolter JR, Alpern M. Typical total monochromacy: a histological and psychophysical study. *Arch Ophthalmol* 1965; 74:610-616.
135. Merin S, Rowe H, Auerbauch E, et al. Syndrome of congenital high myopia with nyctalopia: Report of findings in 25 families. *Am J Ophthalmol* 1970; 70:541-547.
136. Curran RE, Robb RM. Isolated foveal hypoplasia. *Arch Ophthalmol* 1976; 94:48-50.
137. Yoshizumi MO, Thomas JV, Hirose T. Foveal hypoplasia and bilateral 360-degree peripheral retinal rosettes. *Am J Ophthalmol* 1979; 87:186-192.
138. O'Donnell FE Jr, Pappas HR. Autosomal dominant foveal hypoplasia and presenile cataracts: a new syndrome. *Arch Ophthalmol* 1982; 100:279-281.
139. Nelson LB, Spaeth GL, Nowinski TS, et al. Aniridia: a review. *Surv Ophthalmol* 1984; 28:621-642.
140. Oliver MD, Dotan SA, Chemke J, et al. Isolated foveal hypoplasia. *Br J Ophthalmol* 1987; 71:926-930.
141. Howard CW, Smith AG, Warman R. Macular hypoplasia in familial cataracts. *J Pediatr Ophthalmol Strabismus* 1993; 30:176-177.
142. Gregor Z. The perifoveal vasculature in albinism. *Br J Ophthalmol* 1978; 62:554-557.
143. Spedick MJ, Beauchamp GR. Retinal vascular and optic nerve abnormalities in albinism. *J Pediatr Ophthalmol Strabismus* 1986; 23:58-63.

144. Krill AE, Lee GB. The electroretinogram in albinos and carriers of the ocular albino trait. *Arch Ophthalmol* 1963; 69:32-38.
145. Wack MA, Peachey NS, Fishman GA. Electroretinographic findings in human oculocutaneous albinism. *Ophthalmology* 1989; 96:1778-1785.
146. Tomei F, Wirth A. The electroretinogram of albinos (Letter). *Vision Res* 1978; 18:1465-1466.
147. Fagadau WR, Heinemann MH, Cotlier E. Hermansky-Pudlak syndrome: albinism with lipofuscin storage. *Int Ophthalmol* 1981; 4:113-122.
148. Reeser F, Weinstein GW, Feiock KB, et al. Electro-oculography as a test of retinal function: the normal and supernormal EOG. *Am J Ophthalmol* 1970; 70:505-514.
149. Guillery RW. Visual pathways in albinos. *Sci Am* 1974; 230:44-54
150. Guillery RW, Okoro AN, Witkop CJ Jr. Abnormal visual pathways in the brain of a human albino. *Brain Res* 1975; 96:373-377.
151. Kupfer C, Chumbley L, Downer JC: Quantitative histology of optic nerve, optic tract and lateral geniculate nucleus of man. *J Anat* 1967; 101:393-401.
152. Creel DJ, Summers CG, King RA. Visual anomalies associated with albinism. *Ophthalmic Paediatr Genet* 1990; 11:193-200.
153. Creel D, Witkop CJ Jr, King RA. Asymmetric visually evoked potentials in human albinos: evidence for visual system anomalies. *Invest Ophthalmol* 1974; 13:430-440.
154. Creel D, O'Donnell FE Jr, Witkop CJ Jr. Visual system anomalies in human ocular albinos. *Science* 1978; 201:931-933.
155. Carroll WM, Jay BS, McDonald WI, et al. Pattern evoked potentials in human albinism. *J Neurol Sci* 1980; 1776:1-22.
156. Creel D, Spekreijse H, Reits D. Evoked potentials in albinos: efficacy of pattern stimuli in detecting misrouted optic fibers. *Electroencephalogr Clin Neurophysiol* 1981; 52:595-603.
157. Apkarian P, Reits D, Spekreijse H, et al. A decisive electrophysiological test for human albinism. *Electroencephalogr Clin Neurolophysiol* 1983; 55:513-531.
158. Creel D, Boxer LA, Fauci AS. Visual and auditory anomalies in Chediak-Higashi syndrome. *Electroencephalogr Clin Neurophysiol* 1983; 55:252-257.
159. Apkarian P, Shallo-Hoffmann J. VEP projections in congenital nystagmus; VEP asymmentry in albinism: a comparison study. *Invest Ophthalmol Vis Sci* 1991; 32:2653-2661.
160. Brodsky MC, Glasier CM, Creel DJ. Magnetic resonance imaging of the visual pathways in human albinos. *J Pediatr Ophthalmol Strabismus* 1993; 30:382-385.
161. St John R, Timney B. Sensitivity deficits consistent with aberrant crossed visual pathways in human albinos. *Invest Ophthalmol Vis Sci* 1981; 21:873-877.
162. Silver J. Studies on the factors that govern directionality of axonal growth in the embryonic optic nerve and at the chiasm of mice. *J Comp Neurol* 1984; 223:238-251.
163. LaVail JH, Nixon RA, Sidman RL. Genetic control of retinal ganglion cell projections. *J Comp Neurol* 1978; 182:399-422.
164. Webster MJ, Shatz CJ, Silver J. Abnormal pigmentation and unusual morphogenesis of the optic stalk may be correlated with retinal axon misguidance in embryonic Siamese cats. *J Comp Neurol* 1988; 269:592-611.
165. Silver J, Sapiro J. Axonal guidance during development of the optic nerve: the role of pigmented epithelia and other extrinsic factors. *J Comp Neurol* 1981; 202:521-538.
166. Strongin AC, Guillery RW. The distribution of melanin in the developing optic cup and stalk and its relation to cellular degeneration. *J Neurosci* 1981; 1:1193-1204.
167. Guillery RW, Jeffery G, Cattanach BM. Abnormally high variability in the uncrossed retinofugal pathway of mice with albino mosaicism. *Development* 1987; 101:857-867.
168. Colello RJ, Jeffery G. Evaluation of the influence of optic stalk melanin on the chiasmatic pathways in the developing rodent visual system. *J Comp Neurol* 1991; 305:304-312.

169. Guo S, Reinecke RD, Fendick M, et al. Visual pathway abnormalities in albinism and infantile nystagmus: VECPs and stereoacuity measurements. *J Pediatr Ophthalmol Strabismus* 1989; 26:97-104.
170. Shallo-Hoffmann J, Apkarian P. Visual evoked response asymmetry only in the albino member of a family with congenital nystagmus. *Invest Ophthalmol Vis Sci* 1993: 34:682-689.
171. Fitzgerald K, Cibis GW. The value of flash visual evoked potentials in albinism. *J Pediatr Ophthalmol Strabismus* 1994; 31:18-25.
172. Illingworth RS. Delayed visual maturation. *Arch Dis Child* 1961; 36:407-409.
173. Uemura Y, Oguchi Y, Katsumi O. Visual development delay. *Ophthalmic Paediatr Genet* 1981; 1:49-58.
174. Fielder AR, Russell-Eggitt IR, Dodd KL, et al. Delayed visual maturation. *Trans Ophthalmol Soc U K* 1985; 104:653-661.
175. Birch E, Hale L, Stager D, et al. Operant acuity of toddlers and developmentally delayed children with low vision. *J Pediatr Ophthalmol Strabismus* 1987; 24:64-69.
176. McDonald MA, Dobson V, Sebris SL, et al. The acuity card procedure: a rapid test of infant acuity. *Invest Ophthalmol Vis Sci* 1985; 26:1158-1162.
177. Teller DY, McDonald MA, Preston K, et al. Assessment of visual acuity in infants and children: the acuity card procedure. *Dev Med Child Neurol* 1986; 28:779-789.
178. Sebris SL, Dobson V, McDonald MA, et al. Acuity cards for visual acuity assessment of infants and children in clinical settings. *Clin Vision Sci* 1987; 2:45-58.
179. Chandna A, Pearson CM, Doran RM. Preferential looking in clinical practice: a year's experience. *Eye* 1988; 2:488-495.
180. Mayer DL, Beiser AS, Warner AF, et al. Monocular acuity norms for the Teller acuity cards between ages one month and four years. *Invest Ophthalmol Vis Sci* 1995; 36:671-685.
181. Salomão SR, Ventura DF. Large sample population age norms for visual acuities obtained with Vistech - Teller acuity cards. *Invest Ophthalmol Vis Sci* 1995; 36:657-670.
182. Wright KW, Walonker F, Edelman P. 10-diopter fixation test for amblyopia. *Arch Ophthalmol* 1981; 99:1242-1246.
183. Wright KW, Edelman PM, Walonker F, et al. Reliability of fixation preference testing in diagnosing amblyopia. *Arch Ophthalmol* 1986; 104:549-553.
184. Zipf RF. Binocular fixation pattern. *Arch Ophthalmol* 1976; 94:401-405.
185. Westheimer G. Scaling of visual acuity measurements. *Arch Ophthalmol* 1979; 97:327-330.
186. Holladay JT, Prager TC. Mean visual acuity (Letter). *Am J Ophthalmol* 1991; 111:372-374.
187. Rosner B. Statistical methods in ophthalmology: an adjustment for the intraclass correlation between eyes. *Biometrics* 1982; 38:105-114.
188. Preston KL, McDonald MA, Sebris SL, et al. Validation of the acuity card procedure for assessment of infants with ocular disorders. *Ophthalmology* 1987; 94:644-653.
189. Hertz BG, Rosenberg J. Acuity card testing of spastic children: preliminary results. *J Pediatr Ophthalmol Strabismus* 1988; 25:139-144.
190. Adams RJ, Courage ML. Assessment of visual acuity in children with severe neurological impairments. *J Pediatr Ophthalmol Strabismus* 1990; 27:185-189.
191. Courage ML, Adams RJ. Visual acuity assessment from birth to three years using the acuity card procedure: cross-sectional and longitudinal samples. *Optom Vis Sci* 1990; 67:713-718.
192. Hartmann EE, Elis GS, Morgan KS, et al. The acuity card procedure: longitudinal assessments. *J Pediatr Ophthalmol Strabismus* 1990; 27:178-184.
193. Hertz BG, Rosenberg J. Effect of mental retardation and motor disability on testing

with visual acuity cards. *Dev Med Child Neurol* 1992; 34:115-122.
194. Birch EE, Hale LA. Criteria for monocular acuity deficit in infancy and early childhood. *Invest Ophthalmol Vis Sci* 1988; 29:636-643.
195. Fantz RL, Ordy JM, Udele MS. Maturation of pattern vision in infants during the first six months. *J Comp Physiol Psychol* 1962; 55:907-917.
196. Dobson V, Teller DY. Visual acuity in human infants: a review and comparison of behavioral and electrophysiological studies. *Vision Res* 1978; 18:1469-1483.
197. Magoon EH, Robb RM. Development of myelin in human optic nerve and tract: a light and electron microscopic study. *Arch Ophthalmol* 1981; 99:655-659.
198. Abramov I, Gordon J, Hendrickson A, et al. The retina of the newborn human infant. *Science* 1982; 217:265-267.
199. Garey LJ, de Courten C. Structural development of the lateral geniculate nucleus and visual cortex in monkey and man. *Behav Brain Res* 1983; 10:3-13.
200. Atkinson J. Human visual development over the first 6 months of life: a review and a hypothesis. *Human Neurobiol* 1984; 3:61-74.
201. Hendrickson AE, Yuodelis C. The morphological development of the human fovea. *Ophthalmology* 1984; 91:603-612.
202. Birch EE. Infant interocular acuity differences and binocular vision. *Vision Res* 1985; 25:571-576.
203. Trueb L, Evans J, Hammel A, et al. Assessing visual acuity of visually impaired children using the Teller acuity card procedure. *Am Orthopt J* 1992; 42:149-154.
204. Quinn GE, Berlin JA, James M. The Teller acuity card procedure: three testers in a clinical setting. *Ophthalmology* 1993; 100:488-494.
205. Dobson V, Quinn GE, Biglan AW, et al. Acuity card assessment of visual function in the cryotherapy for retinopathy of prematurity trial. *Invest Ophthalmol Vis Sci* 1990; 31:1702-1708.
206. Kushner BJ. Grating acuity tests should not be used for social service purposes in preliterate children. *Arch Ophthalmol* 1994; 112:1030-1031.
207. Abadi RV, Sandikcioglu M. Visual resolution in congenital pendular nystagmus. *Am J Optom Physiol Opt* 1975; 52:573-581.
208. Loshin DS, Browning RA. Contrast sensitivity in albinotic patients. *Am J Optom Physiol Opt* 1983; 6:158-166.
209. Meiusi RS, Lavoie JD, Summers CG. The effect of grating orientation on resolution acuity in patients with nystagmus. *J Pediatr Ophthalmol Strabismus* 1993; 30:259-261.
210. Raye K, Pratt E, Rodier D, et al. Acuity card and grating orientation: acuity of normals and patients with nystagmus. ARVO Abstracts. *Invest Ophthalmol Vis Sci* 1991: 32:960.
211. Bedell HE, Loshin DS. Interrelations between measures of visual acuity and parameters of eye movement in congenital nystagmus. *Invest Ophthalmol Vis Sci* 1991; 32:416-421.
212. Sokol S, Hansen VC, Moskowitz A, et al. Evoked potential and preferential looking estimates of visual acuity in pediatric patients. *Ophthalmology* 1983; 90:552-562.
213. Mayer DL, Fulton AB. Preferential looking grating acuities of infants at risk of amblyopia. *Trans Ophthalmol Soc U K* 1985; 104:903-911.
214. Kushner BJ, Lucchese NJ, Morton GV. Grating visual acuity with Teller cards compared with Snellen visual acuity in literate patients. *Arch Ophthalmol* 1995; 113:485-493.
215. Mayer DL, Fulton AB, Hansen RM. Visual acuity of infants and children with retinal degenerations. *Ophthalmic Paediatr Genet* 1985; 5:51-56.
216. Mayer DL, Fulton AB, Rodier D. Grating and recognition acuities of pediatric patients. *Ophthalmology* 1984; 91:947-953.
217. Jenkins PL, Simon JW, Kandel GL, et al. A simple grating visual acuity test for impaired children. *Am J Ophthalmol* 1985; 99:652-658.

218. Marx MS, Werner P, Fridman P, et al. Visual acuity estimates in the aged. *Clin Vision Sci* 1989; 4:179-182.
219. Marx MS, Werner P, Cohen-Mansfield J, et al. Visual acuity estimates in noncommunicative elderly persons. *Invest Ophthalmol Vis Sci* 1990; 31:593-596.
220. Ferris FL III, Sperduto RD. Standard illumination for visual acuity testing in clinical research. *Am J Ophthalmol* 1982; 94:97-98.
221. Ferris FL III, Kassoff A, Bresnick GH, et al. New visual acuity charts for clinical research. *Am J Ophthalmol* 1982; 94:91-96.
222. Ferris FL III, Kassoff A, Bresnick GH, et al. Visual acuity charts for clinical research. *Am Orthopt J* 1986; 36:14-18.
223. Frank JW. Scaling of visual acuity: applying a logarithmic scale. *Am Orthopt J* 1986; 36:11-13.
224. Teller DY, Morse R, Borton R, et al. Visual acuity for vertical and diagonal gratings in human infants. *Vision Res* 1974; 14:1433-1439.
225. Dobson V, Salem D, Carson JB. Visual acuity in infants: the effect of variations in stimulus luminance within the photopic range. *Invest Ophthalmol Vis Sci* 1983; 24:519-522.
226. Robinson J, Moseley MJ, Fielder AR. Grating acuity cards: spurious resolution and the "edge artifact." *Clin Vision Sci* 1988; 3:285-288.
227. Oguni M, Tanaka O, Shinohara H, et al. Ultrastructural study on the retinal pigment epithelium of human embryos, with special reference to quantitative study on the development of melanin granules. *Acta Anat* 1991; 140:335-342.
228. Mund ML, Rodriques MM, Fine BS. Light and electron microscopic observations on the pigmented layers of the developing human eye. *Am J Ophthalmol* 1972; 73:167-182.
229. Nussbaum JJ, Pruett RC, Delori FC. Historic perspectives. Macular yellow pigment: The first 200 years. *Retina* 1981; 1:296-310.
230. Bone RA, Landrum JT, Tarsis SL. Preliminary identification of the human macular pigment. *Vision Res* 1985; 25:1531-1535.
231. Handelman GJ, Dratz EA, Reay CC, et al. Carotenoids in the human macula and whole retina. *Invest Ophthalmol Vis Sci* 1988; 29:850-855.
232. Yuodelis C, Hendrickson A. A qualitative and quantitative analysis of the human fovea during development. *Vision Res* 1986; 26:847-855.
233. Isenberg SJ. Macular development in the premature infant. *Am J Ophthalmol* 1986; 101:74-80.
234. Deutman AF. *The Hereditary Dystrophies of the Posterior Pole of the Eye*. Assen, Netherlands, Van Gorcum 1971, pp.10-15.
235. Abadi RV, Cox MJ. The distribution of macular pigment in human albinos. *Invest Ophthalmol Vis Sci* 1992; 33:494-497.
236. Yanoff M. Macular pathology. In: Yannuzzi LA, Gitter KA, Schatz H, eds. *The Macula: A Comprehensive Text and Atlas*. Baltimore, Williams & Wilkins, 1979, pp 3-13.
237. Zinn KM, Benjamin-Henkind JV. Anatomy of the human retinal pigment epithelium. In: Zinn KM, Marmor MF, eds. *The Retinal Pigment Epithelium*. Cambridge, Mass, Harvard University Press, 1979, pp 3-31.