Visual System Anomalies in Human Ocular Albinos

Abstract. *Visually evoked potentials recorded from two types of human ocular albinos demonstrated significant hemispheric asymmetry following monocular stimulation. The asymmetry is indicative of disorganization of retinogeniculostriate projections similar to that reported for mammals with total albinism. Abnormal optic projections are associated with lack of ocular pigment and are not associated with any specific generalized pigment defect.*

Since 1965 a wealth of scientific reports have been published demonstrating anomalous uncrossed optic projections in oculocutaneous (total) albinos of nine mammalian species including humans (*1–10*). We have found evidence for a similar anomaly in two genetically distinct types of human ocular albinos, X-linked ocular albinism (*11*) and a newly described autosomal recessively inherited ocular albinism (*12*). The coloration of the skin and hair of both genetic types of human ocular albinos is within the normal range. X-linked ocular albinos have giant melanosomes in skin and hair bulb melanocytes, autosomal recessive ocular albinos have normal-sized melanosomes (*12*). However, both types of ocular albinos have congenital nystagmus, a high incidence of heterotropia, subnormal visual acuity, and hypopigmentation of the uvea and pigment epithelia of the iris, ciliary body, and retina (see cover).

The original hypothesis that differences might exist between the visual systems of an albino and a pigmented mammal was suggested by Sheridan (*1*) when he observed differences in the learning capabilities of albino and ocularly pigmented "split-brain" rats. Lund (*2*) verified an anomalous uncrossed optic system in the albino rat, and Giolli and Guthrie (*3*) extended the finding to the rabbit. Guillery (*4*) first noted the anomalous lamination of the dorsal lateral geniculate in the Siamese cat. This finding prompted Creel (*5*) to point out that the Siamese cat possesses a mutant allele of the albino series at the C tyrosinase locus ($c^h c^h$) and to suggest that there is a genetically determined derangement of the optic fibers of albinic mammals that may be a highly general transspecies phenomenon that includes man. After verification of optic anomalies in albinic varieties of eight species of mammals (*6*), studies of scalp-recorded evoked potentials in oculocutaneous albino humans indicated a similar anomaly in man (*7*). Guillery *et al.* (*8*) have since anatomically verified anomalous optic projections in several brains of human oculocutaneous albinos.

These findings of anomalous optic projections in mammals with various forms of oculocutaneous albinism emphasized the potential importance of normal pigmentation of the optic cup in the embryonic development of the retinogeniculate projections (*9*). If ocular hypopigmentation alone is the necessary correlate with misrouting of optic projections, then human ocular albinos, albeit without extraocular albinism, may have disorganized visual systems.

A series of experiments with rats, guinea pigs, cats, and humans (*5, 7, 9, 10*) have shown that visually evoked potentials (VEP's) recorded from surface electrodes reflect the disorganized uncrossed retinogeniculostriate projections in albinic mammals. The evoked potential technique provides a method for evaluating visual system anomalizes in man as it reflects underlying functional anatomy. By covering one eye and photically stimulating the other, the relative contributions of optic projections from the uncrossed and crossed optic fibers may be compared.

Binocularly evoked potentials are fairly symmetrical between hemispheres in both normally pigmented and albino humans. The coefficients of correlation of their VEP's are usually greater than .90 (*7, 13*). Even when one eye is enucleated in a normally pigmented human, the hemispheric asymmetry is not striking, the difference being a reduction in amplitude of 15 to 20 percent in the uncrossed hemisphere with all components usually present (*14*). Monocularly evoked potentials in most normally pigmented humans show little asymmetry. A significant asymmetry between the evoked potentials recorded from each hemisphere of monocularly illuminated human ocular albinos and those from normally pigmented humans would constitute evidence of anomalous optic projections.

Binocularly and monocularly evoked potentials have been recorded from a number of human oculocutaneous albinos. Using this methodology we have recorded VEP's from more than 50 human oculocutaneous albinos of four types that can be distinguished from each other on the basis of their biochemical, clinical, genetic, and ultrastructural characteristics (*15*). Approximately 70 percent of human oculocutaneous albinos show asymmetry between hemispheres following monocular stimulation with one or more components of the evoked potential missing or significantly attenuated (*7*). The degree of asymmetry of monocularly evoked potentials is significantly greater than that observed in normally pigmented humans with one eye enucleated (*14*), and for most albinos is as severe as that seen in neurologic patients with lesions of the optic pathways resulting in visual field defects.

Even with binocular stimulation it is not unusual to occasionally record asymmetry of evoked potentials between hemispheres in normally pigmented or albino humans. The distinctive feature of the human albino's visual system is the dramatic change in the VEP following monocular stimulation compared to the effects of monocular stimulation in normally pigmented subjects. Monocular stimulation reveals the discontinuity and fragmentation of the retinotopic organization of the albino's visual projections between eye and cortex.

The disorganization of the visual systems of albino mammals is not random. There are an excessive number of optic afferents that cross at the optic chiasma and an insufficient number of optic afferents that do not cross. The misrouted optic fibers originate from approximately the first 20° of the temporal retina. Many of these fibers erroneously cross at the optic chiasma and terminate in a portion of the dorsal lateral geniculate nucleus normally reserved for uncrossed optic afferents. These terminations fragment the normally continuous retinotopic organization of the dorsal lateral geniculate nucleus, subsequently producing a disruption of retinotopically organized projections to striate cortex. This anomalous retinotopic cortical organization is reflected in the form of the VEP.

Some components of the VEP change polarity in normally pigmented subjects when left-right half-field stimulation is used (*16*). The effect of misrouting of optic afferents is similar to shifting the visual field midline (0° meridian) up to 20°. In the albino this shift is analogous to the effect of partial field stimulation in a normally pigmented subject. Misrouting of retinogeniculostriate projections alters the location of cortical generators of potentials. An albino limited to monocular stimulation produces changes in components of the VEP similar to those reported for normally pigmented subjects following partial left-right field stimulation. As one might expect, the changes in components of the VEP of monocularly stimulated human albinos are similar to

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those of patients with homonymous hemianopsia or localized unilateral macular scotoma affecting the first 20° of the horizontal field (*17*).

The subjects of the present study were eight male and two female human ocular albinos. Their clinical and genetic features have been described in previous reports (*12, 18*). Five subjects were whites, three with autosomal recessive ocular albinism and two with X-linked ocular albinism confirmed by skin biopsy (*12*). Five subjects were blacks with X-linked ocular albinism proved by skin biopsy. All ten subjects had nystagmus, heterotropia, and subnormal visual acuity. Visual acuity ranged from 20/400 to 20/50. Ocular pigmentation was variable. Four of the whites and one black had marked iris translucency and marked hypopigmentation of the fundus. The fifth white had weak iris transillumination and a mildly hypopigmented fundus. Each of the other four black subjects lacked iris translucency and had a mildly hypopigmented fundus. All ten subjects, regardless of degree of fundus pigmentation, had hypoplastic foveae as evidenced by absence of normal hyperpigmentation of the fovea, absence of the foveal depressions, and failure of the retinal vessels to wreathe the fovea centralis. This was best appreciated by a dilated fundus examination with indirect ophthalmoscopy. None of these subjects had elevated intraocular pressure, pathologic cupping of the optic nerve head, or optic atrophy. The subjects with amblyopia used their preferred eye when monocular stimulation was required. Pigmentation of their skin and hair was normal, except that several had a mild generalized pigmentary dilution compared to their unaffected siblings.

Electrodes were attached bilaterally to the scalp overlying the visual areas and to each ear (O1-A1, O2-A2) and an electrode linking the subject to earth ground was attached on top of the head at Cz (*19*). An intensity setting of PS1 was used, producing a flash illuminance of approximately 3.0 lux in the darkened room. Brain activity was amplified by a Grass polygraph and monitored in an adjacent room. Sixty flashes were presented at a rate of one flash approximately every 2 seconds; these were averaged by computer and plotted by an X-Y plotter. Binocularly evoked potentials were recorded first. One eye was then covered with layers of opaque material including several adhesive eye patches. The efficiency of the occlusion was checked for each subject. Ten normally pigmented brown-eyed control subjects were tested by the same procedure.

For all subjects except one of the ocular albinos, there were no significant hemispheric asymmetries in the form of the VEP's with binocular illumination. When one eye was then covered and the evoked potentials were again recorded, there were still no significant asymmetries among the ten normally pigmented control subjects, but seven of the ten ocular albinos demonstrated significant hemispheric asymmetry. The evoked potentials recorded from the brown-eyed control subjects were minimally affected by monocular occlusion (Fig. 1B9). Changes were limited to an attenuation in amplitude of approximately 15 percent of the peaks of potentials recorded from the uncrossed hemisphere. In seven of the ten ocular albinos, the potentials evoked by monocular illumination showed one or more components of the evoked potentials as having reversed polarity, missing, or significantly attenuated (Fig. 1, A2 and A7). The components that appear in the first 125 msec in the ocular albinos' evoked potentials were most affected in the hemisphere which receives the uncrossed optic fibers. The asymmetric evoked potentials of both human ocular and total albinos are probably due to disorganization of cortical projections similar to the disorganization reported for the Siamese cat (*20*). The missing components in the uncrossed evoked potential are most likely the result of disorganized geniculostriate projections generating potentials in abnormally oriented areas of the visual cortex.

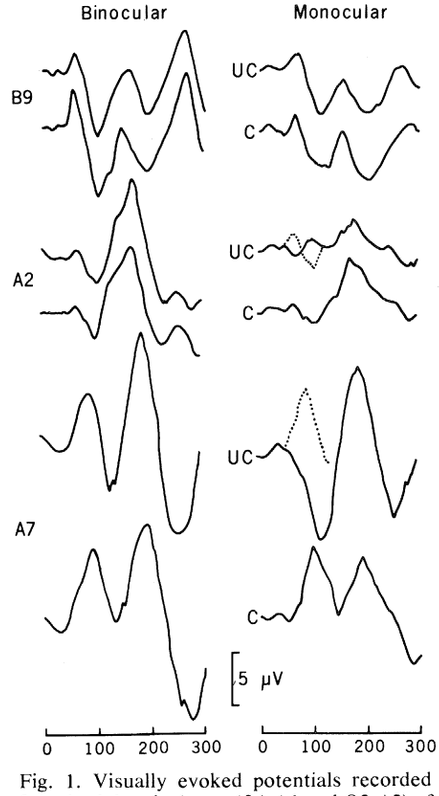

Fig. 1. Visually evoked potentials recorded from both hemispheres (O1-A1 and O2-A2) of a brown-eyed subject (B9) and two ocular albinos (A2 and A7) under conditions of binocular and monocular illumination. Monocularly evoked potentials recorded from the hemisphere receiving the uncrossed (*UC*) optic fibers can be compared to evoked potentials recorded from the hemisphere receiving the crossed (*C*) optic fibers. Components missing from the UC evoked potential are indicated by dotted lines. Horizontal time base, 300 msec; negative is up.

The asymmetric evoked potentials of monocularly illuminated human ocular albinos suggest that there is a disorganization of the uncrossed optic fibers similar to that reported for other albinic mammals. The degree of asymmetry of the monocularly evoked potentials from seven ocular albinos was as severe as that observed in oculocutaneous human albinos. The proportion of ocular albinos exhibiting the asymmetric evoked potentials (70 percent) agrees with the proportion found in oculocutaneous albinism (68 percent), based on evoked potentials recorded from 50 oculocutaneous albinos (*21*).

The insensitivity of the scalp-recorded evoked potential to the subtleties of the visual system, plus anatomic variability, would account for 30 percent of human albinos having normal evoked potentials. There are several sources of anatomic variability. There is the variation in structure of laminae of the human dorsal laterial geniculate nucleus in general. In several albino rats and guinea pigs of inbred strains the laminae of the lateral geniculate nucleus resembled those of pigmented rather than those of albino animals (*9, 10*). Among human albinos, there is probably considerable variation in the retinal point of origin and proportion of uncrossed fibers, in the organization of the geniculate laminae, and in the organization of geniculostriate projections (*20*). Further, the juxtaposition of the cortical generators of the VEP probably varies considerably. The extent of striate cortex varies between hemispheres, as does the infolding of cortical sulci (*22*). Variation in location and orientation of cortical generators would affect the form of scalp-recorded VEP (*16*).

The results of this study suggest that human ocular albinos have abnormal retinogeniculostriate projections, as previously demonstrated in oculocutaneous albinos (*2–11*). Thus, anomalous optic projections are associated with lack of ocular pigment and are not associated with any specific generalized pigment defect. Moreover, these results suggest that the misdirection probably begins

within the retina. A clinical implication of this study is that in contrast to some normally pigmented children with congenital strabismus, where early corrective surgery achieves a moderate degree of binocularity of vision (*23*), infants with ocular albinism would not benefit from surgery to achieve binocular vision, as they lack the neuronal substrate for cortical binocularity.

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Social Inhibition of Maturation in Natural Populations of *Xiphophorus variatus* (Pisces: Poeciliidae)

Abstract. *According to analyses of field samples, social inhibition of maturation is at work in natural populations of the variable platyfish,* Xiphophorus variatus. *In the laboratory, adult males inhibit the maturation of juveniles; the inhibition is overcome as the juveniles increase in size. The proportion of maturing males in any field collection is related to the number of adult males present and the size of the juveniles. The more adults, the fewer maturing males are present; the larger the average juvenile, the greater the number of males maturing. The evolution of this system is best understood in terms of individual selection, but consequences of the system buffer the population against the effects of predation.*

Social interactions can affect the structure of vertebrate populations. Systems in which social inhibitions affect demographic variables such as fecundity (*1*), sex ratios (*2*), and probability of sexual maturation (*3*) have been described. These systems are of interest because they exemplify homeostatic control of demography through behavioral intervention and illustrate the phenomenon of social control over phenotype (*4*).

Laboratory studies have shown that adult size and the timing of maturation in male fishes of the genus *Xiphophorus* are under social control (*3*). A larger juvenile inhibits a smaller one from maturing, but is not inhibited in turn. The inhibiting fish matures early and stops growing, whereas the inhibited fish continues to grow until reaching a size sufficient to overcome the inhibition. At that point it matures and stops growing, us-

Table 1. Some characteristics of *X. variatus* populations. These characteristics change from year to year and are related. The table lists mean size ($\bar{X}$) of and relative size difference between juvenile (j) and transforming (t) males $[(X_t - X_j)/\bar{X}]$ (for samples with more than five of each), the relative proportion of adult males $[P_a/(1 - P_a)]$, and the proportion of transforming males (P_t) for 15 different samples of two populations taken over a 10-year period. The proportion of adults is the number of adult males divided by the total number of males. The number of transforming males divided by the total number of nonadult males is P_t.

Sample	Sample size	$\bar{X}$ (mm)	$(X_t - X_j)/\bar{X}$	$P_a/(1 - P_a)$	P_t
		Encino			
Big pool					
1970	59	24.30	0.146	1.681	0.273
1973	101	19.86	0.148	1.294	0.182
1974	31	26.43	0.052	1.066	0.400
Upper pool					
1973	30	21.48		1.500	0.333
1975	50	20.16	0.124	0.667	0.300
Lower pool					
1975	31	19.28		1.584	0.333
		Sarco			
Pool 1					
1973	87	24.43	0.131	1.174	0.550
1975	124	23.99	0.156	1.584	0.479
1977	67	27.07	0.129	1.793	0.667
Pool 3					
1977	30	20.58		1.309	0.154
Pool 6					
1967	92	19.95	0.056	0.261	0.342
1973	33	21.02	0.020	0.138	0.793
1977 (upper)	74	21.13	0.078	0.848	0.525
1977 (lower)	71	23.71	0.105	1.451	0.414
Pool 9					
1967	23	20.49		1.083	0.364

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