the location of as yet unidentified crossed axons, the clinical neurologic findings following destruction of one lateral half of the third cranial nerve nucleus may be similar.

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REFERENCES


Electrophysiologic evidence for normal optic nerve fiber projections in normally pigmented squinters. GLEN L. McCORMACK.

The Siamese cat, a type of albino, has a visual pathway anomaly in which too many optic nerve fibers cross at the optic chiasm, and also frequently has strabismus. The correlation of strabismus with this defect suggests that a similar pathway defect without pigmentation anomalies, may be the cause of much human strabismus. Creel, Witkop, and King have used evoked potential methods to show that such a pathway defect likely occurs in the human albino. While unpublished control experiments verified their results on human albinos, no such defect has been found in the normally-pigmented human squinters. It is concluded that the visual pathway anomaly is limited to albimism and is not a likely cause of most human strabismus.

The causes of human squint (strabismus) are usually unknown, especially in terms of specific neurologic models. In a rather small percentage of cases, pathologic or mechanical factors can be shown to be the primary cause. In most cases, however, no demonstrable pathologic or mechanical involvement can be found which would be significant enough to cause strabismus. These cases usually fall under the broad classification known as "concomitant" squint, a classification which would include a possible cause of strabismus which is to be tested here. Since anatomic or physiologic research is reasonably quite limited in human squinters, it is necessary to look toward animal studies for possible models of human strabismus. It is true, however, that naturally occurring squint in binocular animals other than man is virtually nonexistent, so any binocular animal showing such a squint deserves consideration as a model for human squint. The Siamese cat is one such animal.

In 1974, Guillery described the unusual visual pathway defect of Siamese cats in which ganglion cell axons arising from the central temporal hemiretinas of each eye cross at the optic chiasm instead of taking the normal ipsilateral course. Since all visual centers in the Siamese cat's brain receive mismatched retinotopic inputs from the eyes, the binocular vision necessary to maintain ocular alignment would presumably not be available, and squint would be predicted. Squint does in fact occur very commonly in Siamese cats, and would seem to be of the concomitant type described above. Mechanical adhesions in the periorbital adnexa do occur in some Siamese cats, but they are the exception and are not frequent enough to explain the incidence of squint in Siamese cats.

The Siamese cat would then seem to be a potentially good model for concomitant human squint, but a difficulty in the viability of this model for the human arises from the fact that

*Concomitant strabismus can be defined as that class of strabismus where the angle of deviation between the eyes does not change in the various directions of gaze. While "accommodative" strabismus is technically included in this definition, this report is not directed toward accommodative strabismus.
this visual pathway defect appears to be almost always associated with albinism (the Siamese cat is a type of albinio) while the human squinter is rarely so. Consequently, it should be shown that the inheritance of albinism can occur independently, at least at the phenotypic level, from the occurrence of the visual pathway defect. As suggested above, the visual pathway defect has been shown to occur in other albinos, and these studies suggest that the pathway defects can occur somewhat independently of the pigmentation defects in albinism. Guillery\(^4\) has shown that flecked mice have essentially normal optic nerve projections despite a patchwork of pigmented and nonpigmented retinal areas. In addition, Westenberg and Giolli\(^5\) have studied a strain of albino mice which have no pathway defect. Most importantly, Giolli and Creel\(^6\) have shown that hooded rats (derived by crossing normally pigmented and albino rats) have visual pathway defects analogous to, but less severe than, their albino parent, despite a normal ocular pigmentation. These studies indicate that the relationship of pigment formation and optic nerve fiber growth specification must be very complex, and that these two factors do not necessarily covary. It seemed possible, therefore, that the human may have also developed the inheritance of such a visual pathway defect, and independently of obvious pigmentation defects. A search for such a visual pathway defect in pigmented human squinters thus was indicated.

Finding evidence for this defect in the human is not an easy task, especially at the anatomic level. Polyan\(^7\) has commented on the irregularities that can occur in the human lateral geniculate lamination, but these irregularities, while suggestive of the unusual lamination pattern of the lateral geniculate nuclei (LGN) in Siamese cats, do not in themselves prove that optic nerve fibers have gone errant. Psychophysical and eye movement methods can provide very sensitive analysis of many visual functions, but it would seem to be presumptive to infer the projection of ganglion cell axons to the LGN from subjective or eye movement responses possibly arising from several orders of neural hierarchy beyond the LGN. The visual evoked response, however, may be able to assess the possibility of such an anatomic defect at the level of the striate cortex, an early stage in visual processing. Creel and co-workers\(^8\) have used the visual evoked response on Siamese cats and human albinos to reveal the presence of the visual pathway defect. Since each eye projects predominantly to the opposite cortical hemisphere in the presence of the visual pathway defect, significant left-right asymmetries would be expected in the distribution of the visual evoked response over the occipital scalp when left-eye stimulation is compared to right-eye stimulation. Conversely, in a normal cat or human subject the scalp distribution of evoked potential would be expected to be approximately the same for either eye (disregarding the monocular crescents of the visual fields) reflecting the anatomic correspondence of the eyes in the cortex. Creel and co-workers did in fact demonstrate evoked potential asymmetries in Siamese cats and human albinos, which suggests similar visual pathway defects in albinos of these two species. I have used the evoked potential method, with a more extensive electrode array (to be described in this report) and have confirmed Creel's result on human albinos (unpublished observations). This report presents the results of these methods applied to normally pigmented squinters.

Pattern stimuli (40 msec; appearance of 14 minute checks from a diffuse field with no net luminance change) were presented from a centrally fixated 13-degree circular field. Subsequent testing was also done with a 52-degree field with no change in results. Average pattern luminance was 49 fL, with a check contrast of 80 per cent.
Jeffreys and Axford\textsuperscript{4} used a stimulus very similar to that just described, and have demonstrated a component occurring 70 to 100 msec (depending on the subject tested and stimulus conditions) after pattern appearance onset which would seem to be generated in striate cortex. The identification of this component as a striate response can be made by comparison of its empirically determined topography on the scalp with a theoretically calculated topographic distribution of evoked potential. This theoretical distribution is obtained by considering the evoked potential generator as the integrated effect of active dipole sheets conforming to those portions of active striate cortex. Control experiments conformed to Jeffreys and Axford's observations and the reader is referred to their report for further detail.

An array of ten electrodes was used to pick up the evoked potential from this stimulus, and the amplitude of the striate component of each was measured relative to the baseline. Four electrodes were placed in a longitudinal array along the midline, separated by 4 cm., with the lower most electrode being on the inion. Six more electrodes, separated by 2.5 cm. each, were placed along a transverse line symmetrical about the first longitudinal electrode above the inion (Fig. 2, lower right). The recording was essentially monopolar with the reference electrode for the ten scalp electrodes being on one ear, and the ground on the other. The electroencephalograms (EEG's) from the ten electrodes were recorded simultaneously and stored on magnetic tape for later analysis. The appropriate number of averages taken per visually evoked response (VER) was determined empirically, on-line, before the recording of data on magnetic tape. The averaged VER was recorded for 300 msec. following stimulus onset.

Fig. 2. Transverse scalp distribution of evoked potentials for normal subject, MT, and squinters, CE, LF, BM, MS, and RS. RS is the exotrope. The electrode configuration used for all subjects is shown in lower right, in same scale as evoked potential graphs. The ordinate on each graph indicates the amplitude of response in microvolts. Solid line represents right eye and broken line the left eye in graphs A, C, D, E, F, and G. Dash-dot line represents the right hemifield of right eye, and the dotted line the left hemifield of the right eye in graph B.
Five normally pigmented squinters, four esotropic, and one exotropic were selected so as to have good acuity in each eye. The five squinters had "congenital" squint (occurring earlier than three years of age), and varying degrees of suppression and anomalous correspondence. While squint and amblyopia are often associated, the frequent occurrence of squint (typically alternating) without amblyopia is in itself a fact indicative that the mechanism of squint is primary. It seemed best, therefore, to avoid the question of amblyopia and the complexities it might produce in the visual evoked response.

Subjects ranged in age from 18 to 34 years. Monocular visual fields in all subjects were full and normal, and all subjects were free of eye pathology. Refractive errors were corrected before testing, with all testing being monocular.

In Fig. 1 is shown the right eye evoked potential recorded from the central electrode of the array for the six subjects. The vertical line through each one indicates the measured component. Figs. 2, A and B show the results of these methods on normal subject, MT. Amplitude of the striate component is plotted as a function of position across the occipital scalp (positive up). The curves have been interpolated between the seven points (corresponding to the seven transverse electrodes) measured. The remaining three electrodes in the longitudinal array are not included as they added little information. In Fig. 2, A the basic experiment is shown, with the solid line indicating the right eye's response, and the broken line the left eye's response. It can be seen that the evoked response topography for the two eyes is virtually the same, reflecting the normal anatomic correspondence of the eyes in the visual cortex. The evoked response topography between individuals can be expected to vary considerably, like the variable morphology of the underlying cortex. This morphology is a major factor determining the topography of the evoked response. Fig. 2, B shows the results of an experiment where the right and left hemifields (indicated by dash-dot and dot lines, respectively) of one eye were stimulated separately in the same normal subject. The topography of the evoked response from these two areas of the visual field is very different, reflecting the fact that the evoked responses have been generated in two spatially distinct areas of the cortex—the right and left hemispheres. This result is important when considering the visual pathway defect in the Siamese cat which has up to 40 degrees of the central visual field represented entirely in the opposite cortical hemisphere. Such an extensive defect occurring in these normally pigmented squinters could produce evoked response topographies analogous to hemifield stimulation in the normal, despite fixation on the center of the circular stimulus field. This result would be expected because of the limited field size used here.

Figs. 2, C through G show the results from the five normally pigmented squinters, fixating the center of the stimulus field. It is immediately evident that these squinters have virtually the same evoked response topography from the right and left eyes. This matching of evoked response topographies suggests that the retinotopic mappings of the eyes on the cortex is the same. Indeed, I have seen little information in the monocular evoked responses from this group which would distinguish them from normal, as one might expect from their good monocular vision.

From the results shown above, it does not appear that the visual pathway defect found in albinos (including the human) occurs outside of the condition of albinism. While five tested squinters cannot speak for all cases of concomitant squint, these cases were selected to represent the "typical" squint in sign and symptom (with the exception of amblyopia) and the results should be applicable to the vast majority of concomitant squint squints. It could be argued though that some form of reorganization of the visual input has occurred, or that the anomalous projection has been limited to small segments of the peripheral retinas, either of which would make the visual pathway difficult to detect. In regards to the former argument, the defect would be indeed difficult to detect if this reorganization occurred, but then such a successful reorganization of the visual afferents would not be expected to produce strabismus either. In regards to the second argument, the methods used here should be sensitive enough to detect visual pathway anomalies much less severe than any known to occur in the Siamese cat, and it is highly unlikely that a visual pathway defect small enough to avoid detection by these methods would cause strabismus.

It seems apparent then that no visual pathway defect is likely to occur in the human without albinism, and it follows from this that the visual pathway defect is not a good model for most human concomitant strabismus.

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The effects of acetazolamide on the human electroretinogram. BIANCA STANESCU AND JEAN MICHELS.

The effects of acetazolamide on the cerebral circulation and metabolism was previously shown to be due to a raised Pco2 in brain tissue. The effects of the drug on the human electroretinogram (ERG) are investigated in fifteen human volunteer subjects. A significant increase in the b-wave was found. A similitude with the mechanism of acetazolamide administration in brain and retinal tissue seems to be a possible explanation.

Up to date, retinal electrogenesis is not definitively explained. The early receptor potential seems to be in relation with photochemistry and the late receptor potential is considered an event at the cellular level. The intracellular recordings showed that the visual cells generate the late receptor potential, resembling the a-wave of the electroretinogram (ERG) and the Muller cells generate a late potential similar to the b-wave.

However, it is difficult to explain how Muller cells, which are glial cells and without synaptic connections with other retina neurons, are able to reply to photic stimulation. It was suggested that Muller cells, as other glial cells, have a high potential of membrane and therefore are very sensitive to the concentration of K ions. The light-activated neurons in the retina, lead to an increase in external K+ which induce the depolarization of the Muller cell and therefore the apparition of the b-wave on the ERG. The purpose of the present study was to study the alterations of the human ERG following retinal metabolic modifications. To induce them we used Diamox, a carbon anhydrase inhibitor, which produces modifications of the acid-base balance and ion metabolism.

The effect of Diamox (acetazolamide) on the human ERG was not previously investigated. Materials and methods. Fifteen subjects with an age range between 18 and 58 years were studied. All had a normal ophthalmologic examination (visual acuity, Goldmann perimetry,ophthalmoscopy). We administered Diamox, 500 mg, intravenously, in 5 c.c. of physiologic serum to all fifteen subjects.

The control group was formed by ten normal ocular subjects, whose ages ranged between 8 months and 53 years. Five cubic centimeters of physiologic serum was administered to this group intravenously.

Blood samples were taken for ionograms before and five minutes after acetazolamide administration.

The ERG record was performed on a cathode ray storage oscilloscope, Tektronix 5103 N, with a polaroid camera connected to an Ahrend van Cogh electroretinograph and its photostimulator. The recording was performed in "Ganzfeld" with a single-flash stimulation on intensity II of our photostimulator.

The "Ganzfeld" was realized by home-made translucent electrodes. The tests were performed in mesopic conditions (750 Lux). The ERG recordings (six stimulations for each record) were performed 5, 10, and 15 minutes before and after the administration of acetazolamide and physiologic serum.

The mean value of the six stimulations for each record was calculated.

Results. In both groups we found a spontaneous decrease in the amplitude of the b-wave which attained maximum level 15 minutes after the start of the experiment.

However, the mean value of the b-wave in both groups at 15 minutes was not statistically different from the mean value at the beginning (P > 0.10).

A progressive increase of the b-wave amplitude followed the administration of acetazolamide in all subjects investigated. The b-wave started to increase five minutes after injection and increased further five minutes later (Fig. 1).

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