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Amblyopia resulting from penalisation: neurophysiological studies of kittens reared with atropinisation of one or both eyes

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SUMMARY Atropinisation of the eyes—a clinical method of treating strabismus called 'penalisation'—in developing kittens caused a reduction in the spatial resolving power of cells in the lateral geniculate nucleus driven by the penalised eye, regardless of whether 1 eye or both eyes had been atropinised. However, binocularity of cells in the visual cortex was reduced only in monocularly penalised cats. It appears that sharply focused foveal images are important in the development of good visual acuity but synergy of the inputs to the 2 eyes is required for the development of binocular vision.

Atropine, a muscarinic receptor-blocking agent, instilled in the conjunctiva of the eye, is used extensively in ophthalmology for dilating the pupil and eliminating accommodation (atropine cycloplegia). For an atropinised eye vision is somewhat blurred due to the loss of accommodative power and to spherical and chromatic aberrations of the lens and light scatter in the ocular media. Atropine is sometimes used for treating children with strabismus by regular application, for a period of time, to the non-strabismic eye to produce blurring of vision in that eye, in order to force the child to use the strabismic or 'lazy' eye. This method of treatment is aptly named 'penalisation', and is aimed at improving visual acuity in the strabismic eye and to achieve binocular vision (Haase, 1976).

Strabismic amblyopia has previously been regarded as being due to the absence of binocular vision, being attributed to lack of competition for synaptic connections on binocularly driven cortical cells (Hubel and Wiesel, 1965; von Noorden, 1973) and possibly also to a tonic inhibitory influence from the visual cortex on inputs from the strabismic eye—'cortical suppression theory' (Lambroso *et al.*, 1969). However, Ikeda and Wright (1972a, 1974) suggested that the amblyopia due to bilateral hypermetropia, anisometropia, and strabismus can be caused by a common factor, i.e., by habitual exposure of the fovea to defocused images during the sensitive period of early postnatal life.

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If blurred retinal images can be the cause of amblyopia as claimed by Ikeda and Wright (1972a, 1974), then defocused images alone without any disturbance of synergy of the inputs to the 2 eyes should cause poor vision, as in the bilateral amblyopia due to bilateral hypermetropia. To examine this possibility we have employed the atropine instillation technique to produce a blurred image in one or both eyes of young kittens. When the kittens reached adult age, single-cell recordings were made from the visual cortex to determine the degree of binocularity and from the lateral geniculate nuclei (LGN) to measure the visual acuity of individual nerve cells.

The kittens with only one eye atropinised will see well-focused images of objects of interest with the non-atropinised eye and a somewhat blurred visual world with the atropinised eye. Thus, the synergy of the inputs to the 2 eyes is impaired, although, unlike the experiments with stimulus deprivation, the atropinised eye receives plenty of visual stimulation, and, unlike the strabismic eye, the retinal correspondence is not disturbed. On the other hand, the synergy of the inputs to the 2 eyes is not disturbed at all in the kittens with both eyes atropinised, even though vision is blurred.

Material and methods

KITTENS

Five kittens born in a specific pathogen-free cat colony were raised with their mother. From the 21st to 23rd day after birth daily application of

1 to 2% atropine sulphate eye drops to one eye of 3 kittens and both eyes of 2 kittens were begun. They were weaned at 6 weeks of age.

The colony room was illuminated by two time-controlled fluorescent tubes (60 W each, 6 a.m. to 8 p.m.) and the kittens received plenty of visual stimulation. Intraocular pressure was measured by a Perkins tonometer to check the unwanted effects of atropine, and the kitten's eyes were ophthalmoscopically examined weekly. Simple behavioural tests (Ikeda and Wright, 1972b), i.e., pupillary reflex, blink reflex, visually guided paw-placing reflex, following target with eye and head movement, used to assess visuo-motor functions were also carried out monthly.

When they reached the age of 5 to 8 months they were subjected to neurophysiological experiments.

NEUROPHYSIOLOGICAL EXPERIMENTS

At 5 to 8 months of age in each kitten recordings of cell activity were carried out in Area 17 of the left and right hemispheres of the visual cortex and also in layers A and A1 of the left and right lateral geniculate nucleus (LGN) using glass microelectrodes filled with 1% pontamine blue in 0·5 M sodium acetate lowered through an agar filled chamber placed over the craniotomy. The kittens were surgically prepared under thiopentone sodium BP (60 mg/kg intraperitoneally). The trachea and femoral vein were cannulated and two craniotomies made at A6·5, L9·0 and A6·5, R9·0 for the LGN recording, and one at P4·5, L0·0 for cortical recording. The cat was maintained under light anaesthesia by artificial ventilation with a gas mixture containing 70 to 80% N_2O, 19 to 28·5% O_2 and 1 to 1·5% CO_2. A mixture containing gallamine triethiodide (7 to 10 mg/kg) and benzylpenicillin (4 to 7 mg/ml) in 2·5% dextrose saline was infused into the femoral vein at the rate of 5 ml/kg h. The end-expired CO_2, electrocardiogram (ECG), and electroencephalogram (EEG) were monitored throughout the experiment to check the physiological condition of the animal. The end-expired CO_2 was maintained at 5% by adjusting the stroke volume of the artificial ventilation pump. The EEG was used to monitor the level of anaesthesia, which was maintained by adjusting the gas mixture accordingly. The body temperature was kept at 38·5°C by a thermostatically-controlled heating blanket.

The positions of the area centralis and optic disc for each eye were determined at the plane of stimulation 57 cm from the eye by using the light beam of an ophthalmoscope reflected back on to a tangent screen.

During single-cell recording the non-atropinised eye was dilated by atropine (1% in water) and the nictitating membrane retracted by phenylephrine hydrocholoride (phenylephrine eye drops BPC). A contact lens with an artificial pupil of 3 mm diameter was placed in both eyes, so that the conditions of the stimulation were identical for both eyes. The eyes were refracted by retinoscopy and supplied with correction lenses to ensure sharp focusing of stimuli on the retina.

Since the kittens had to be maintained in good physiological condition under continuous anaesthesia for 3 days in order to obtain data from both left and right hemispheres of the visual cortex as well as the LGNs, we had to apply a strict time schedule together with painstaking attention to the animal's condition. The first day was allocated to recording from the visual cortex, the second day to recording from the left (or right) LGN, and the third day to the right (or left) LGN. In order to obtain satisfactory recordings throughout the 3 days no data were collected during the period 1 a.m. to 8 a.m. We have found that cells recorded during this time are often sluggish in their responses, with the EEG exhibiting considerable slow wave activity. For this period the level of anaesthesia was deepened, the infusion rate reduced to 2·5 ml/kg h, and the room darkened.

RECORDING AND STIMULATION OF CORTICAL CELLS

Sampling of cells in the visual cortex was carried out according to the following strict protocol. For each cat 3 penetrations were made in each hemisphere at stereotaxic co-ordinates P3·5, P4·5, and P5·5 and 1 mm lateral to the midline, all penetrations being terminated at a depth of 2 mm from the cortical surface. We routinely recorded 6 to 8 cells in each penetration, thus sampling about 20 cells in each hemisphere of each animal.

All cells recorded from the visual cortex (Area 17) had receptive fields within 2° of the visual axis. Receptive field properties of visual cortical neurones were studied conventionally using flashing or moving bars or slits of light, altering the length, width, and orientation of the slit to elicit an optimal response (Hubel and Wiesel, 1962; 1965). For each cell the receptive field properties were determined by stimulating each eye separately. Cell responses were measured by constructing post-stimulus histograms with an averaging computer (Biomac 1000) over 16 stimulation cycles.

RECORDING AND STIMULATION OF LGN CELLS

The receptive field position and properties of LGN cells were studied using flashing spots of light. The spatial resolution of each cell was measured using gratings with a sinusoidal luminance profile of progressively increasing spatial frequency. Spatial

frequency is the number of light and dark lines appearing within one degree of visual angle. The mean luminance of the gratings was 10 cd/m² and the contrast of the light and dark lines was 0·4. Each grating was moved so that a pair of light and dark lines travelled across the receptive field centre within 1 s. Each LGN cell gives a train of spikes when either the light line (if the cell is on-centre) or dark line (if the cell is off-centre) passes the receptive field centre, giving distinct modulation of firing. The method is fully described elsewhere. All cells were studied under monocular viewing conditions.

Results

CONDITION OF KITTENS IN THE ALERT STATE BEFORE THE NEUROPHYSIOLOGICAL EXPERIMENTS

Intraocular pressures were measured in all 5 kittens. Values ranged from 14 to 20 mmHg in the non-atropinised eyes as well as in the atropinised eyes. This range of values was also obtained from other kittens in the same colony not treated with atropine. The corneas and ocular media of the eyes treated with atropine maintained their usual transparency. Furthermore, no misalignment of the eyes was observed. This was checked during the experiment under anaesthetised and paralysed conditions using the light beam reflected back through an ophthalmoscope to locate the area centralis (Ikeda and Wright, 1976; Ikeda *et al.*, 1977). The atropinised eyes did not reveal any measurable squint. Before the experiment there was no consistent difference in the refractive state of the normal and atropinised eyes as determined by the ophthalmoscope. This was confirmed by accurate retinoscopy when the kittens were anaesthetised and paralysed for the experiment.

No kittens showed any significant impairment of vision when tested by simple behavioural tests, e.g., tracking eye movements, contact placing reflexes, jumping from a height for food, etc. (Ikeda and Wright, 1972b). However, the pupillary light reflex was abolished in all the atropinised eyes. The kittens' performance at tracking a small object (a pencil at 57 cm from the eyes) was tested with an opaque contact lens placed on the non-atropinised eye of the monocularly atropinised kittens. Using just their atropinised eye, they tended to lose the pencil easily and their behaviour was generally sluggish compared with their performance when tested with the non-atropinised eye. It was difficult to assess the behaviour of the bilaterally atropinised kittens, since no comparison could be made between the eyes, although their tracking of a small pencil at 57 cm seemed to be less precise compared with normal cats using one or both eyes.

SPATIAL RESOLUTION OF LGN CELLS

At both the left and right LGN the spatial resolution of cells was measured by finding the highest spatial frequency (finest light and dark lines) of grating of sinusoidal luminance profile to which the cell responded with modulated firing, just distinguishing the contrast of the lines. The classification of cells into 'X' or 'Y' by the 'null position' test of Enroth-Cugell and Robson (1966) was not carried out, but all cells included in the study were classified into either 'sustained' or 'transient' cells, using a stationary optimal spot located at the receptive field centre (Fukada, 1971; Cleland *et al.*, 1971; Ikeda and Wright, 1972c). Those cells which gave sustained firing to a stationary spot located at the receptive field centre, on for 20 s (on-centre cell) or while the spot was off for 20 s (off-centre cell), were classified as 'sustained' and those which gave only transient firing to such a stimulus as 'transient' cells.

The results from kittens raised with one eye atropinised are shown in Fig. 1, and those from the kittens with both eyes atropinised, in Fig. 2. In these figures the highest spatial frequencies of the grating stimulus to which 'sustained' and 'transient' cells responded with modulated firing were plotted against the eccentricity of the receptive field position.

For both 'sustained' (Fig. 1 *left*) and 'transient' (Fig. 1 *right*) cells those cells driven from the normal eye at or near the area centralis showed the highest resolution, and this gradually fell to a lower level as eccentricity increased. The slope is much sharper for 'sustained' cells than for 'transient' cells. For cells driven by the atropinised eye the spatial resolution was much poorer than for the non-atropinised eye at or near the visual axis, and the difference between the two eyes declined as the eccentricity increased. Although this observation was applicable for both 'sustained' and 'transient' cells, the loss of spatial resolution was much greater in the 'sustained' cells driven from the atropinised eye.

The picture in Fig. 2, which shows the results from the kittens raised with both eyes atropinised, is different from that of Fig. 1. There is no difference here between the cells driven by the left eye or right eye. The spatial resolution of the LGN cells receiving inputs from the area centralis zone was poor for both eyes. Since these results were obtained under artificial pupils of 3 mm diameter in all eyes and with refractive error correction, they reflect entirely neural events.

BINOCULARITY OF VISUAL CORTICAL CELLS

All cells encountered had qualitatively normal receptive field properties such as orientation tuning and directional specificity, and could be classified as

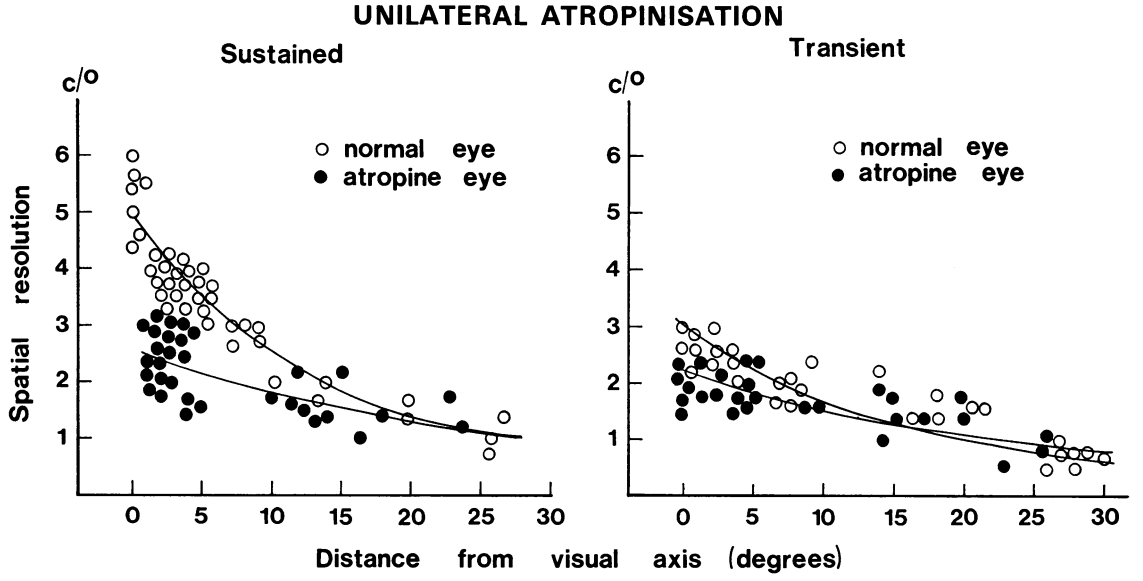

Fig. 1 *Plot of spatial resolution of 'sustained'* (left) *and 'transient'* (right) *cells in the LGN driven by the non-atropinised right eye* (open circles) *and the atropinised left eye* (filled circles) *against retinal eccentricity. The vertical axis, c/° (cycles per degree), indicates spatial frequency of the finest grating (expressed in number of light and dark line pairs in 1° of visual angle) which is resolved by each cell. The lines drawn through the points are least-squares best-fit curves. The two curves for the 'sustained' cells are significantly different ($P < 0{\cdot}01$), whereas those for the 'transient' cells are not. There was, however, a significant difference in spatial resultion between 'transient' cells driven by the normal and atropininised eye from within 5° of visual axis ($P < 0{\cdot}01$)*

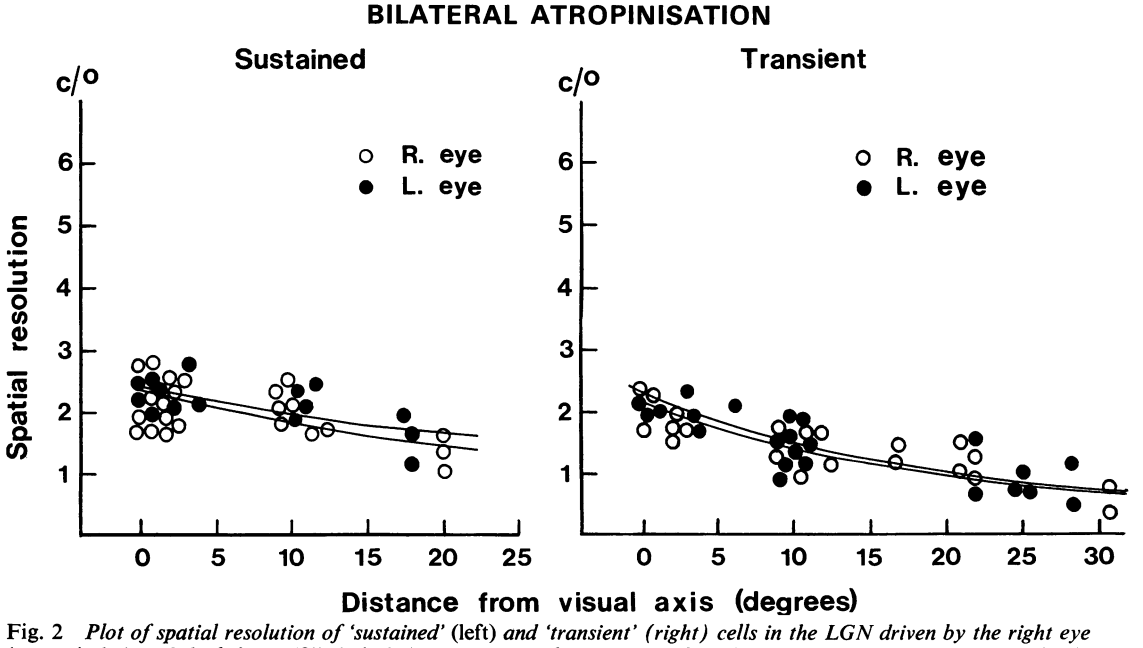

Fig. 2 *Plot of spatial resolution of 'sustained'* (left) *and 'transient' (right) cells in the LGN driven by the right eye* (open circles) *and the left eye* (filled circles) *against retinal eccentricity from kittens with both eyes atropinised. The vertical axis, c/° (cycles per degree), indicates spatial frequency of the finest grating (expressed in number of light and dark line pairs in 1° of visual angle) which is resolved by each cell. The lines drawn through the points are least-squares best-fit curves. In both 'sustained' and 'transient' graphs the 2 curves are not significantly different*

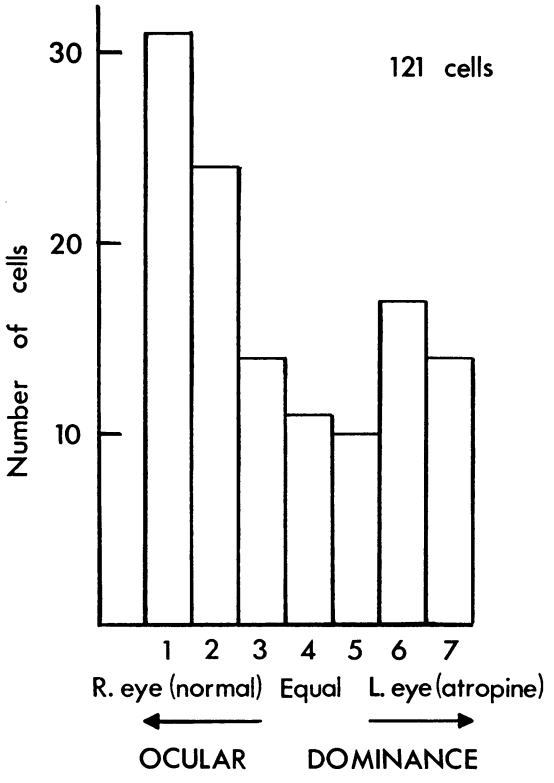

Fig. 3 *Number of visual cortical cells in each of the 7 ocular dominance groups obtained from 3 kittens raised with 1 eye atropinised. Cells were sampled from both hemispheres according to a strict protocol: 6 electrode penetrations to a depth of 2 mm at stereotaxic co-ordinates P3·5, P4·5, P5·5, and 1 mm left and right of the midline in each kitten. Group 1 consists of cells driven by the right eye (non-atropinised) only, group 4, those driven equally by both eyes, and group 7, those driven by the left eye (atropinised) only*

simple or complex cells. However, our emphasis in this investigation was placed on the ocular dominance pattern.

In accordance with the method of Hubel and Wiesel (1962; 1965) the visual cortical cells were analysed by the degree of binocularity of their inputs—that is all cells were classified according to whether the cell received inputs predominantly from the contralateral eye or ipsilateral eye or equally from both eyes.

Fig. 3 shows the ocular dominance pattern of the visual cortical cells in the kittens raised with 1 eye atropinised. The ocular dominance pattern of the cells from the kittens with both eyes atropinised is shown in Fig. 4.

Of a total of 121 cells obtained from the 3 monocularly atropinised kittens 62 cells were recorded from the left hemisphere and 59 cells from the right hemisphere (see Methods section).

The ocular dominance groups in Fig. 3 are slightly different from those shown by Hubel and Wiesel (1962, 1965). Data from both hemispheres were combined so that group 1 consists of cells exclusively driven by the non-atropinised eye, and group 7 contains those cells exclusively driven by the atropinised eye, regardless of whether the cells were recorded from the contralateral or ipsilateral hemisphere. In groups 2 and 3 cells were driven predominantly by the non-atropinised eye (group 2 more so than group 3), while groups 5 and 6 contain cells driven predominantly by the atropinised eye (group 6 more so than group 5). Cells in group 4

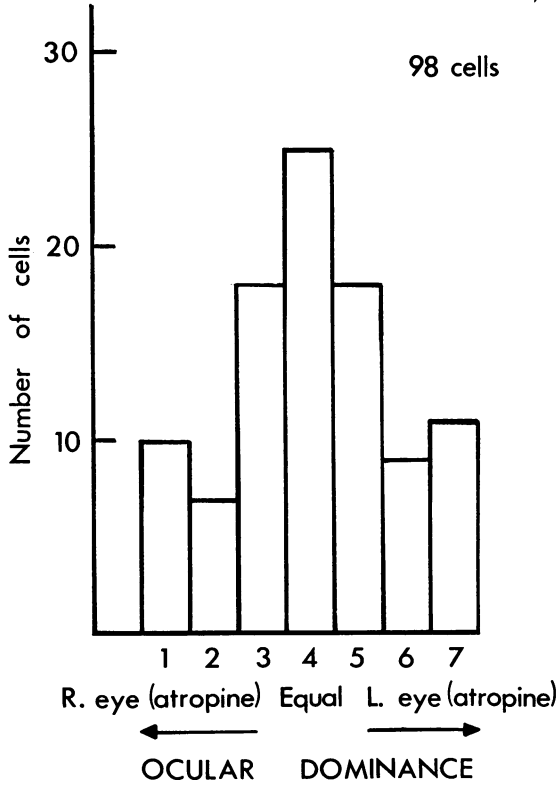

Fig. 4 *Number of visual cortical cells in each of the 7 ocular dominance groups obtained from the 2 kittens raised with both eyes atropinised. Cells were sampled from both hemispheres according to a strict protocol: 6 electrode penetrations to a depth of 2 mm at stereotaxic co-ordinates P3·5, P4·5, P5·5, and 1 mm left and right of the midline in each kitten. Group 1 consists of cells driven by the right eye (atropinised) only, group 4, those driven equally by both eyes, and group 7, those driven by the left eye (also atropinised) only*

were driven approximately equally by both eyes (the spike count per stimulus differing by less than 4 between eyes). As Fig. 3 shows, the kittens raised with one eye atropinised showed a reduction in the number of cells in groups 3, 4 and 5 indicating that a greater proportion of visual cortical cells were monocularly driven. There was a general trend of the ocular dominance histogram to shift towards the non-atropinised eye (despite the fact that an approximately equal number of cells were sampled from the left and right hemispheres).

Of the total of 98 cells obtained from the 2 kittens with binocularly atropinised eyes 56 cells were recorded from the left hemisphere and 42 from the right hemisphere. In Fig. 4 the combined data from both hemispheres are shown. Here group 1 consists of cells driven exclusively by the right eye and group 7 those driven only by the left eye. Groups 2 and 3 contain cells driven predominantly by the right eye, whereas groups 5 and 6 consist of those driven predominantly by the left eye. As before, group 4 consists of cells driven equally by the left and right eye. Fig. 4 shows that the ocular dominance pattern of the visual cortical cells in the kittens raised with both eyes atropinised maintained the proportions shown by normal cats (Hubel and Wiesel, 1962; 1965). Approximately 62·2% of cells were in groups 3, 4, and 5 receiving binocular inputs.

Discussion

We found that the spatial resolving power of cells in the LGN—particularly 'sustained' cells—which received inputs from the area centralis of the atropinised eye was reduced. The reduction of spatial resolution (our measure of visual acuity of cells) was found in all atropinised eyes regardless of whether one eye only (Fig. 1) or both eyes (Fig. 2) had been atropinised during the sensitive period of development. Thus the cells fed by the area centralis of the atropinised eyes were amblyopic. Since the intraocular pressure, refraction, and ocular alignment had not been affected by atropine, the effect that we observed on the spatial resolution of LGN cells must have been due to the pharmacological actions of atropine, i.e., paralysis of accommodation, and dilatation of the pupil causing blurred images on the retina.

The degree of 'blur' caused by paralysed accommodation will depend upon the distance of the object from the eye. The 'blur' will be practically nil for objects at 'infinity' and will increase as the object is brought close to the eye. In practice the maximum blurring will be equivalent to a defocusing by 4 to 8 D, which is the maximum accommodative power found in young kittens.

We have previously shown that a defocused image is an inappropriate stimulus for 'sustained' retinal ganglion cells (Ikeda and Wright, 1972; 1974). 'Sustained' cells in the visual pathway receiving inputs from the area centralis of the retina cease to respond entirely to a stimulus defocused by 8 D, whereas, 'transient' cells continue to respond to defocused stimuli with transient firing. Thus it is not surprising that blurring of the retinal image by atropinisation, regardless of whether the blur was present in one eye or both eyes, could lead to a loss of 'visual acuity' of those 'sustained' cells which had been deprived of adequate stimulation. It should be noted that the 'amblyopia' demonstrated in LGN cells fed by the atropinised eyes was a change in spatial resolution from 6′ of arc line discrimination to 12′ of arc line discrimination. This change is equivalent to a loss of visual acuity from 6/6 to 6/12.

Further evidence that the reduced visual acuity (amblyopia) occurs independently of the degree of cortical binocularity and that amblyopia is due to blurred retinal images present during the critical period of development comes from our data on experimental strabismus (Ikeda and Tremain, 1977). We found that kittens reared with esotropia in one eye produced amblyopia but those reared with exotropia in one eye did not, although cortical binocularity was reduced in both conditions. Our exotropic kittens showed alternating fixation but our esotropic kittens did not. Thus the area centralis of the exotropic eye received clearly focused images during the critical period of development, whereas the esotropic eye received blurred images of objects at different distances from the fixation plane, which was entirely determined by the fellow normal eye. These experimental esotropic and exotropic conditions may be considered as clinical homologues of strabismic amblyopia. The bilateral amblyopia found in kittens reared with bilateral atropinisation may be a clinical homologue of binocular hypermetropia, whereas the unilateral amblyopia found in monocularly atropinised kittens simulates anisometropia.

We found that cortical binocularity was reduced in the monocularly atropinised kittens and the ocular dominance pattern slightly shifted towards the non-atropinised eye (Fig. 3), but was normal in the binocularly atropinised kittens (Fig. 4), despite the fact that these eyes were slightly amblyopic.

The effect of monocular atropinisation on the ocular dominance pattern is much weaker than the effect of monocular deprivation or strabismus (Wiesel and Hubel, 1963; 1965; Baker *et al.*, 1974; Blakemore and Van Sluyters, 1974; Yinon *et al.*, 1975; Yinon, 1976), and even less than the effect of rearing the kitten with a translucent diffuser over

one eye, thus depriving it of patterned stimulation completely (Wiesel and Hubel, 1963; Blakemore, 1976).

Blakemore (1976) reported a loss of binocularity in cats raised with a neutral density filter of 2 log units covering 1 eye. Thus the neutral density filter reduces the retinal illumination and contrast by 100-fold. Atropine applied to the eye, on the other hand, causes an opposite effect. It increases the retinal illumination by approximately 10-fold. Nevertheless, in our experiments the effect of monocular atropinisation on cortical binocularity was similar to that of the neutral density filter over 1 eye shown by Blakemore (1976). These observations led to the conclusion that, regardless of whether the illumination was raised or lowered in 1 eye during the sensitive period of development, the binocularity of cortical cells was much reduced, whereas when the retinal illumination of both eyes was raised by an equal amount the binocularity was maintained. This may be used as further evidence for Hubel and Wiesel's theory that synergy of the inputs to both eyes is essential for achieving binocularly driven cells at the visual cortex (Hubel and Wiesel, 1965).

Furthermore, our results provide further evidence that amblyopia and loss of binocularity have separate causes, as we stated previously (Ikeda and Tremain, 1977). Amblyopia results from habitual exposure of the fovea to blurred images during the critical period of postnatal development (Ikeda and Wright, 1972a; 1974; von Noorden, 1974), whereas loss of binocular vision results from the lack of synergy of the inputs from the 2 eyes to the visual cortex (Hubel and Wiesel, 1965; Blakemore, 1976). The former lesion is probably in the lower visual pathway before information from the 2 eyes is mixed at the cortex, while the latter lesion is at the geniculocortical synapse.

The clinical significance of these results is that the method of treating strabismic children by 'penalisation' of the good eye with atropine (if used without any additional lenses) might be expected to produce the very defects in the 'penalised' eye which it aims to prevent in the 'lazy' strabismic eye, if it is performed during the sensitive period of development. Von Noorden (1977), in fact, has mentioned the danger of continuous penalisation, although penalisation of the normal eye with near vision corrected, thus giving the normal eye sharply focused images of near objects, has been successful in treating amblyopia in hypermetropic or anisometropic children (Ron and Nawratzki, 1977). It appears that refractive and strabismic errors of the eyes should be corrected in infants as early as possible to prevent amblyopia in later life.

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