Original Articles

Experimental amblyopia in monkeys. Further behavioral observations and clinical correlations*

Gunter K. von Noorden

The effects of unilateral lid closure and artificial esotropia on the development of visual acuity were studied in visually immature rhesus monkeys (Macaca mulatta). Irreversible amblyopia occurred in all animals whose lids were sutured between birth and nine weeks of age. Lid closure at the age of 12 weeks did not produce amblyopia. During the age of susceptibility only brief periods of occlusion (two to four weeks) were effective in causing severe amblyopia. Strabismic amblyopia occurred in monkeys in which the onset of experimental esotropia was during the first week of life. Correlation of these data with those obtained from human patients indicate that the human visual system remains sensitive to unilateral lid closure for a longer period of time than that of the monkey. Clinical observations also suggest that, as in monkeys, unilateral occlusion for only brief periods during infancy may cause irreversible amblyopia and, therefore, is contraindicated.

Key words: amblyopia, monkeys, primates, lid closure, visual deprivation, experimental strabismus, visual acuity, esotropia.

We have reported in earlier publications that amblyopia can be induced in rhesus monkeys by unilateral lid suture and artificial esotropia during visual immaturity.[1, 2] From these investigations we concluded that the critical age at which unilateral lid suture will cause loss of visual acuity must lie between birth and the third month of life, but were unable to pinpoint more precisely this age of susceptibility to visual deprivation. With the testing equipment used in these studies, we were able also to determine visual acuity to a level of only 20/140, which precluded the diagnosis of milder degrees of amblyopia that may have been present in animals in which the eye was occluded after the age of 3 months.

In the continuation of our study of the behavioral aspects of experimental am-
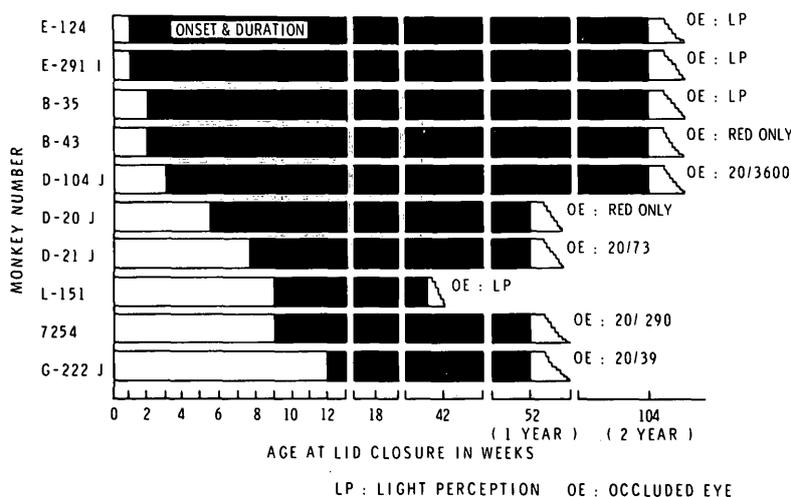
Fig. 1. Age and duration (long-term) of lid closure and visual acuity.

blyopia in monkeys, the apparatus was modified to permit testing of visual acuity to a 20/39 level, and the period of susceptibility to unilateral visual deprivation can now be delineated more exactly. We have found also that the visual system of the monkey is extraordinarily sensitive to brief periods of unilateral lid closure during this period. The purpose of this study is to report these findings and to correlate our results with clinical observations in humans with amblyopia.

Material and methods

Unilateral lid closure was performed in 15 rhesus monkeys *(Macaca mulatta)* between the first and twelfth week of life. In 10 animals the eye was closed for periods ranging from 12 to 24 months. In five monkeys the lid was opened after two to four weeks in order to study the effects of short-term visual deprivation. Esotropia was produced in three additional monkeys at the ages of 1, 7, and 92 days.

The surgical techniques for lid closure, the artificial production of esotropia, and details regarding the testing apparatus and training procedure were described in earlier papers.[1, 2] The only change in method of training in this study was to increase the working distance from 14 to 140 cm., which permitted testing of visual acuity with Landolt rings to a level of 20/39.

Training was begun at ages ranging from 7 to 25 months. Once the test criterion was reached, i.e., the animal recognized Landolt rings in their smallest optical reduction, the lids of the previously open eye were sutured together and the

closed eye was opened. Visual acuity testing was resumed with the visually deprived or deviated eye. The details regarding the age at which the lids were closed and the duration of visual deprivation are summarized in Figs. 1 and 2.

Results

The data in Fig. 1 on the effects of long-term unilateral lid closure on visual acuity show that the age of susceptibility to unilateral visual deprivation in rhesus monkeys lies between birth and the ninth week of life. Lid closure at the age of 12 weeks did not produce amblyopia, and visual function in the formerly deprived eye returned rapidly and completely after closure of the sound eye. Most animals were retested after periods of 6 to 24 months. During this time the use of the amblyopic eye was enforced by suturing the lids of the sound eye. Not a single animal recovered visual acuity.

Several animals whose lids were sutured during the sensitive period not only were unable to recognize the largest Landolt ring (corresponding to a visual acuity of 20/3600) but also failed to respond to presentation of large red circles. We have not yet determined whether this apparent additional loss of red sensitivity in the deprived eye is significant or whether it represents total lack of further cooperation from the severely visually handicapped
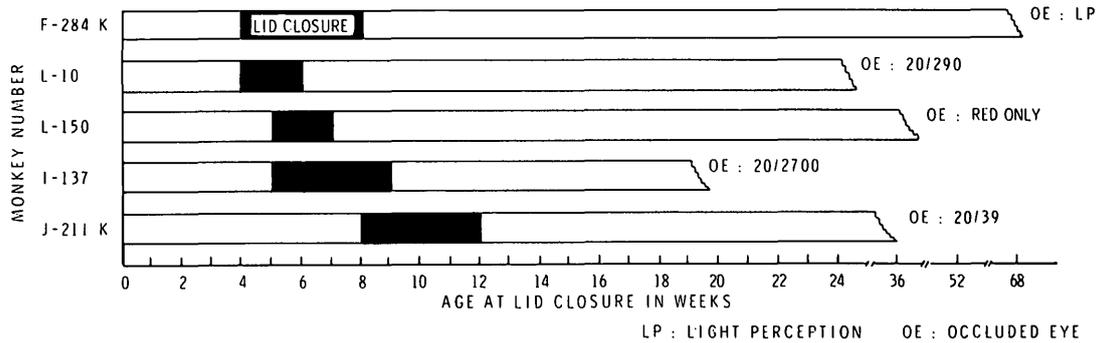
Fig. 2. Effect of short-term lid closure on visual acuity.

animal after suturing the lids of the sound eye.

The data also show that apparently individual differences exist in the susceptibility of the visual system to unilateral lid closure, for one animal (D21J) had less severe amblyopia even though his lids were closed at an earlier age (7½ weeks) than another animal (7254) which became severely amblyopic after lid closure at the age of 9 weeks.

The effects of short-term unilateral lid closure are shown in Fig. 2. These data indicate that just a brief period (two to four weeks) of unilateral visual deprivation during visual immaturity will cause severe amblyopia. Lid closure for two weeks caused less severe amblyopia than four weeks of occlusion. Lid closure of four weeks during the end of the sensitive period (8 to 12 weeks) had no effect on the development of normal visual acuity. Upon retesting these animals after enforced usage of the previously deprived eye, recovery of visual acuity was not evident.

Data on behavior in animals with strabismic amblyopia are summarized in Table I. As was the case in the animals with unilateral lid suture, amblyopia developed only when esotropia was induced within the first three months of life, which suggests that the period of sensitivity of the visual system to abnormal visual stimulation is similar for both forms of amblyopia. Improvement but not normalization of visual acuity occurred only in one monkey (E293) after enforced use of the deviated

Table I. Effect of experimental esotropia on visual acuity

Animal No.	Age at surgery (days)	After closure of sound eye	Retested after 2 years
B 37 I (VDM 4)	1	Light perception	Light perception
E 293 (VDM 6)	7	Light perception	20/360
L 152	92	20/39	

eye by suturing the sound eye. Previous experiments had shown that the onset of strabismic amblyopia in monkeys, as in humans, depends upon the age at which strabismus occurred and on the unilaterality of the deviation. Amblyopia did not develop in one monkey in which alternating exotropia occurred on the seventh day of life.[2]

Discussion

Our data show that the period during which an animal is susceptible to the effects of monocular occlusion begins at birth and ends by the time the monkey has reached the age of 12 weeks. We have also demonstrated that during this time just a brief period of monocular occlusion will cause a permanent defect in visual acuity. The period of susceptibility for the development of strabismic amblyopia is less well defined, but thus far our observations indicate that it may be similar to that for visual deprivation amblyopia.

The severe behavioral changes in our monkeys corresponded well with neurophysiologic anomalies of the visual cortex[3]

and with histologic alterations in the lateral geniculate nuclei (LGN).[4]

The question arises whether amblyopia reflects an arrest of development of visual function when the animal is deprived of normal visual experience early in life or is the result of disruption of visual functions that are present at birth. Since it has been established that visual acuity in newborn rhesus monkeys may be as high as 9 to 36 minutes of arc,[5] and since the degree of amblyopia in our animals was considerably more profound than one would expect on the basis of arrested development, we are inclined to favor the second view. Hubel and Wiesel[6] arrived at similar conclusions after demonstrating in newborn kittens that visual functions may be highly organized without the benefit of previous visual experience.

The finding that only brief periods of unilateral occlusion during visual immaturity may cause severe, irreversible behavioral defects in the adult monkey is of special interest. Hubel and Wiesel[7] have shown in kittens that unilateral occlusion for as little as three or four days during the period of high susceptibility, which is similar to that in monkeys, can cause severe neurophysiologic anomalies in the visual cortex. In fact, the reduction in the number of cortical neurons from the deprived eye that could be stimulated was comparable to that observed after three months of monocular deprivation from birth. We have not yet performed the neurophysiologic experiments in these monkeys, but in view of previously established severe neurophysiologic anomalies in the monkey's visual cortex, one would expect to arrive at similar results as after longer periods of deprivation.[3]

In view of the similarity between the organization of the visual system in monkeys and humans, correlation of the results of our experiments with clinical observations in humans is of special interest. It is well known that amblyopia ex anopsia develops during infancy in humans

during deprivation of normal retinal image formation because of obstacles such as ptosis, prolonged uncontrolled occlusion, dense corneal opacities, and mature, congenital, and traumatic cataracts.[8] The clinician is aware that if such conditions are present from birth or develop during early childhood, irreversible amblyopia will persist despite surgical correction of the underlying condition and prolonged enforced usage of the amblyopic eye.

The age of onset, cause, and duration of visual deprivation, and final visual acuity in a group of patients personally observed by the author are listed in Table II. The patients with traumatic cataracts had 20/20 media and normal fundi after aspiration of the lens. These data show that amblyopia ex anopsia following unilateral visual deprivation can occur in children as old as 52 months, even though additional clinical observation is necessary to delineate more precisely the human age of susceptibility to unilateral visual deprivation. Using puberty, the completion of growth in length, and the life-span as criteria for comparison,[9] one year in the life of a monkey (*M. mulatta*) corresponds to approximately three years of human life. Thus, the human visual system for unknown reasons appears to be sensitive to the effects of unilateral deprivation for a considerably longer period of time than that of the macaque.

Although longer periods of unilateral visual deprivation in humans are known to cause irreversible amblyopia, the question arises whether the human visual system responds similarly to that of the monkey to brief periods of occlusion. Alerted from our monkey experiments, we have recently observed three patients in whom a similar mechanism may have been a factor in causing the amblyopia:

Case 8. This 6-year-old girl recently failed a vision-screening test in school. The initial history provided by her mother was essentially negative. Visual acuity was O.D. 20/60, O.S. 20/20. The child was

Table II. Stimulus deprivation amblyopia in humans

Case No.	Age at onset	Cause	Duration (months)	Visual Acuity*
1	Birth	Tarsorrhaphy	6	4/200
2	Birth	Hemangioma of upper lid	12	1/200
3	Birth	Ptosis	15	20/200
4	3 months	Tarsorrhaphy	12	10/200
5	26 months	Traumatic cataract	48	1/200
6	42 months	Traumatic cataract	60	2/200
7	51 months	Traumatic cataract	12	20/200

*Best corrected.

emmetropic, and a complete ophthalmologic examination failed to reveal the cause of her amblyopia. Four months of constant occlusion of the left eye was ineffective in improving visual acuity of the right eye. Upon further questioning, the mother recalled that the child had sustained a corneal scratch in the right eye at the age of 2 months which was treated with antibiotics and continuous patching of the right eye for a four-week period.

Case 9. This 3-year-old girl had left esotropia since the age of 3 months. Her history revealed that she had been returned from the newborn nursery with purulent conjunctivitis and marked swelling of the lids of the left eye. At the age of 3 months and after extensive antibiotic therapy, lid swelling subsided and the mother was able to see the pupil for the first time. She stated that the eye had deviated inward ever since. There was no family history of strabismus. Ocular examination revealed a visual acuity of 20/30 in the right eye and hand movements in the left eye. On covering the right eye, the left eye made searching, nystagmoid movements. Cycloplegic refraction: +1.00 sph. O.U. Except for a left esotropia of approximately 40Δ, the remainder of the ophthalmologic examination was normal. This child has consistently refused to wear a patch over the right eye.

Case 10. This 7-year-old girl had failed a school vision test. She had a history of hemangioma involving the left upper lid which was noted shortly after birth. The pupil remained exposed, however, until 12 months of age, at which time the tumor had enlarged to such an extent that the left eye was totally covered for three months. The tumor was removed by a plastic surgeon at the age of 15 months and the eye has remained open ever since. Her visual acuity was 20/20 in the right eye and 20/70 in the left eye. The remainder of the ophthalmologic examination, including refraction, failed to reveal the cause for her amblyopia. The amblyopia did not respond to constant occlusion of the sound eye for a period of three months.

These data indicate that unilateral lid closure for only brief periods of time in infants may indeed be harmful and should be avoided since visual acuity of the occluded eye may become permanently affected. Awaya and co-workers[10] have made similar observations. Although occlusion amblyopia, as it occasionally develops in the formerly dominant eye of older children up to the age of 5 years during treatment of strabismic amblyopia, as a rule is reversible,[11-15] such may not be the case in infants. For this reason, we no longer occlude the dominant eye of children under 2 years with strabismus for more than one week without re-examining the patient. If longer periods of occlusion are required to improve stability of fixation of the deviated eye, we advocate switching the patch to the amblyopic eye for two days each week in order to enforce use of the occluded eye. Likewise, the advisability of treating external eye disease with an eye patch in infants should be re-evaluated in view of our findings.

REFERENCES

1. von Noorden, G. K., Dowling, J. E., and Ferguson, D. C.: Experimental amblyopia in monkeys. I. Behavioral studies of stimulus deprivation amblyopia, Arch. Ophthalmol. 84: 206, 1970.
2. von Noorden, G. K., and Dowling, J. E.: Experimental amblyopia in monkeys. II. Behavioral studies in strabismic amblyopia, Arch. Ophthalmol. 84: 215, 1970.
3. Baker, F. H., Grigg, P., and von Noorden, G. K.: Effects of visual deprivation and strabismus on the response of neurons on the visual cortex of the monkey, including studies on the striate and prestriate cortex in the normal animal, Brain Res. In press.
4. von Noorden, G. K.: Histological studies of the visual system in monkeys with experimental amblyopia, INVEST. OPHTHAL. Submitted.
5. Ordy, J. M., Samorajski, T., Collins, R. L., et al.: Postnatal development of vision in a subhuman primate (*Macaca mulatta*), Arch. Ophthalmol. 73: 674, 1965.
6. Hubel, D., and Wiesel, T. N.: Receptive fields of cells in striate cortex of very young, visually inexperienced kittens, J. Neurophysiol. 26: 994, 1963.
7. Hubel, D. H., and Wiesel, T. N.: The period of susceptibility to the physiological effects of unilateral eye closure in kittens, J. Physiol. 206: 419, 1970.
8. von Noorden, G. K., and Maumenee, E. A.: Clinical observations on stimulus deprivation amblyopia (amblyopia ex anopsia), Am. J. Ophthalmol. 65: 220, 1968.
9. Schultz, A. H.: Postembryonic age changes. In Primatologia Hofer, H., Schultz, A. H., and Starck, D., editors: Basel, 1956, S. Karger, vol. 1, p. 891.
10. Awaya, S., Miyake, Y., Imaizumi, Y., et al.: Amblyopia in man, suggestive of stimulus deprivation amblyopia, Jap. J. Ophthalmol. 17: 69, 1973.
11. Costenbader, F. D.: Strabismus. In Ophthalmic Symposium No. II. St. Louis, 1958, The C. V. Mosby Company, p. 484.
12. Hardesty, H. H.: Occlusion amblyopia; report of a case, Arch. Ophthalmol. 62: 314, 1959.
13. von Noorden, G. K.: Prophylaxis of amblyopia, J. Pediatr. Ophthalmol. 1: 35, 1964.
14. Burian, H. M.: Occlusion amblyopia and the development of eccentric fixation in occluded eyes, Am. J. Ophthalmol. 62: 853, 1966.
15. von Noorden, G. K.: The etiology and pathogenesis of fixation anomalies in strabismus, Trans. Am. Ophthalmol. Soc. 67: 698, 1969.