

The Permanence of the Visual Recovery that Follows Reverse Occlusion of Monocularly Deprived Kittens

Donald E. Mitchell, Kathryn M. Murphy, and Martin G. Kaye

While the behavioral and physiologic effects of an early period of monocular deprivation can be extremely severe, they are not necessarily irreversible. Considerable recovery can occur if visual input is restored to the deprived eye sufficiently early, particularly if the nondeprived eye is occluded at the same time (reverse occlusion). This study examines the permanence of the visual recovery promoted by a period of reverse occlusion in kittens that were monocularly deprived from near birth for periods ranging from 3 to 18 weeks. During the period of reverse occlusion, the vision of the initially deprived eye improved from apparent blindness to good levels of acuity. However, upon restoring visual input to the formerly nondeprived eye a surprisingly rapid and reciprocal change occurred in the visual acuity of both eyes. Much of the substantial gain in the vision of the initially deprived eye that occurred during reverse occlusion was lost within 3 weeks, while at the same time the vision of the initially nondeprived eye improved substantially. Nevertheless, in many animals the acuity of the initially nondeprived eye did not recover to levels it had reached prior to reverse occlusion. These results hold important implications for the nature of the mechanisms responsible for the dramatic physiologic effects of monocular occlusion and reverse occlusion on the visual cortex. The results also may help elucidate recent observations on patching therapy in human amblyopia. Invest Ophthalmol Vis Sci 25:908-917, 1984

The behavioral and physiologic consequences of early monocular deprivation by eyelid closure have been explored extensively in both cats and monkeys.^{1,2} Following this form of early visual deprivation, the overwhelming majority of cells in the visual cortex can be excited only by visual stimulation of the nondeprived eye.³⁻⁵ This striking shift in the ocular allegiance of cortical cells in favor of the nondeprived eye is accompanied by severe deficits of form vision in the deprived eye.^{6,7} Equally profound visual deficits have been reported in humans that had experienced a severe peripheral impediment (such as a cataract) to patterned visual input to one eye in early life⁸⁻¹¹ (deprivation amblyopia¹²). The striking anatomic and physiologic changes observed in the central visual pathways of monocularly deprived cats and monkeys not only provide an insight into the origins of the severe visual deficits associated with deprivation amblyopia, but also into the origins of the more mild deficits found in other forms of amblyopia where the early embarrassment to concordant visual imagery in the two eyes is likely to be less severe.

Despite the severity of the behavioral and physiologic deficits that follow early monocular deprivation, significant recovery can occur if normal visual input is restored to the deprived eye sufficiently early.^{4,13} Considerable recovery even occurs in the cat by simply opening the eyelids of the deprived eye, thereby restoring simultaneous visual input to both eyes.¹⁴ However, in macaque monkeys virtually no behavioral or physiologic recovery is observed in this situation.^{15,16} Measureable, functional recovery in this species only has been reported following reverse occlusion, when at the time that visual input is restored to the deprived eye, the nondeprived eye is occluded.^{16,17} Although this procedure is not necessary to initiate recovery in cats, it nevertheless promotes greater physiologic recovery in the visual cortex and frequently better visual acuity in the deprived eye than occurs when both eyes are open during the recovery period.¹⁴ Because of its resemblance to conventional patching therapy for human amblyopia, we have initiated a detailed study of the effectiveness of reverse occlusion as a means of promoting visual recovery in the deprived eye of monocularly deprived kittens. As a first step, we have examined the permanence of the visual recovery promoted by a period of reverse occlusion in animals that were monocularly deprived from near birth for various lengths of time. Surprisingly, most of the substantial visual gain made during the period of reverse occlusion was lost quickly (within 3 weeks) once visual input was restored to both eyes, a finding that provides an

From the Psychology Department, Dalhousie University, Halifax, Nova Scotia, Canada.

Supported by grant AP-7660 (DEM) from the National Sciences and Engineering Research Council of Canada.

Submitted for publication: July 25, 1983.

Reprint requests: Dr. Donald E. Mitchell, Psychology Department, Dalhousie University, Halifax, Nova Scotia, B3H 4J1, Canada.

insight into the nature of the mechanisms that underlie the anatomic and physiologic changes that occur during reverse occlusion. A brief account of some of these findings has been presented elsewhere.¹⁸

Materials and Methods

Animals and Rearing Conditions

The 10 kittens of nonspecific breed that participated in this study were all born and raised in a closed animal colony. At about the time of natural eye-opening (8–12 days), one eyelid of each kitten was sutured closed under halothane anesthesia. The lid margins were removed and the palpebral conjunctivae pulled away from the wounded lid margins. Chloromycetin ointment was placed around the wounded lid margins, which were then sutured together. Upon termination of the initial period of monocular deprivation, the lids of the deprived eye were parted carefully while those of the nondeprived eye of nine animals were sutured closed for a period of time that differed for each animal (Table 1). This operation, as well as the similar one conducted on termination of the period of reverse occlusion, was performed with the animal anesthetized with a mixture of ketamine and xylazine supplemented with gaseous halothane.

Behavioral Testing

Measurements were made of the visual acuity of the two eyes using the jumping stand described earlier.^{7,19,20} The animals were trained on this apparatus to jump onto a square-wave grating that was placed beside a uniform field of the same size and mean luminance (about 100 cd/m²). The lateral position of the two stimuli was interchanged between trials according to a pseudo-random schedule. If the animal jumped onto the grating, it was rewarded with food (puréed chicken liver) and petting. Incorrect jumps to the adjacent uniform field were punished by simple denial of the rewards. Training on this discrimination was begun at 4–5 weeks of age or at least a month before the period of reverse occlusion. This was usually completed in only 3–4 days following which measurements of visual acuity were commenced using a simple modification of the procedures described earlier. The spatial frequency of the grating was increased by a small amount between successive blocks of trials until a spatial frequency was reached where the animal could no longer attain criterion performance. The highest spatial frequency on which the animal was able to sustain criterion performance on one or more repetitions of this procedure was defined as the acuity on that particular session. The most significant change that was made to this general procedure was to alter the size and nature

Table 1. Rearing histories of the nine monocularly deprived kittens subjected to a period of reverse occlusion

Kitten name	Initial period of monocular deprivation			Reverse occlusion		
	From (days of age)	To (days of age)	Period (days)	From (days of age)	To (days of age)	Period (days)
C158	8	28	20	28	49	21
C141	11	35	24	35	73	38
C136	8	41	33	41	85	44
C115	12	66	54	66	101	35
C94	9	94	85	94	183	89
C124	10	94	84	94	182	88
C125	10	101	91	101	203	102
C117	10	103	93	103	194	91
C137	8	134	126	134	192	58

of the increments in spatial frequency between blocks of trials so that they were both small and equal in size on a logarithmic scale (12 steps to the octave). While this change to the procedure required that the number of different spatial frequencies that were tested on any given session be increased, at the same time it permitted the number of trials on each block to be reduced. In general, we found that even experienced animals performed best if the trials, on any given session, began with gratings of very low spatial frequencies, which were incremented in small but uniform steps between successive blocks of trials. We typically employed only one or two trials for gratings that were more than an octave above the suspected cut-off spatial frequency and increased the number of trials in each block to 3 or 5 within an octave of this threshold. In order for the spatial frequency of the grating to be increased after a given block of trials, the animals had to meet at least one of three criteria. Performance had to be either flawless on that particular block of trials, or following an error, the animal had to make five consecutively correct responses or at least seven correct responses from a maximum of ten trials. If none of these criteria could be met within the maximum 10 trials, the spatial frequency of the grating was reduced by at least an octave until the animal could achieve criterion performance once more, after which the spatial frequency was incremented as before. This simple modification to the procedure produced a surprising improvement in the accuracy and repeatability with which acuity could be specified. It was typical for animals to pass from flawless to chance performance with only a 6% or 12% change in spatial frequency. The highest spatial frequency for which criterion performance was achieved on a given session was taken as the acuity for that day. All calculations of spatial frequency were corrected for the amount the animal leaned prior to jumping. As discussed in detail in earlier

publications,^{7,19,20} this procedure allows rapid and highly repeatable estimates of visual acuity after only a few training sessions.

The grating stimuli, which were prepared for this study by photographic enlargement of Ronchi rulings (2 to 4 lines/mm), had a Michelson contrast of 1.0. Both the grating and uniform gray stimuli were large (19.5×19.5 cm, surrounded by a 3.5-cm black border) so that they subtended 15.5×15.5 deg from the typical jumping height (70 cm) that was employed for kittens over 2-months-old. For all but the animals that initially were deprived to 4 or 5 weeks of age, measurements of the acuity of the nondeprived eye were made each day until the period of reverse occlusion. The recovery of vision in the deprived eye was documented by regular testing throughout the period of reverse occlusion. Upon restoration of binocular visual input measurements of the monocular acuity of the two eyes were made at regular intervals with the eye that was not tested covered with a large opaque contact lens occluder. Because of possible corneal distortions that may temporarily follow wearing of these occluders, we did not attempt to measure the monocular acuity of both eyes on the same day. Measurements of the acuities of the deprived and nondeprived eyes therefore were made on successive days. However, in certain animals, estimates of the acuities of both eyes were made on the first day following termination of reverse occlusion. On these occasions, the acuity of the initially deprived eye was derived from measurement of the binocular visual acuity, which previous work⁷ has shown to reflect the acuity of the better eye. This was a safe assumption here since the other (initially nondeprived) eye was typically blind at this time.

Measurements of the contrast sensitivity for sinusoidal gratings were made on one of the kittens using a jumping stand that was modified specifically for the purpose. The stimuli were presented on the face of a large oscilloscope display monitor (Joyce Electronics; Cambridge, England), which was turned so that its face pointed upwards and viewed through a sheet of plate glass that formed the landing surface of the jumping stand. By suitably gating the signal to the Z axis of the oscilloscope, it was possible to present a stationary grating on either half of the screen and a uniform field of the same mean luminance on the other half. A thin wooden divider was placed on the glass landing surface of the jumping stand between the two stimuli. As before, the cat was required to jump to the grating; between blocks of trials the Michelson contrast was reduced in 1-dB steps. The stimuli had a luminance of 90 cd/m^2 , and at the observation distance of 57 cm were 20 deg high and 14 deg wide. As a consequence, only about 3.5 cycles of the grating were visible at the lowest spatial frequency tested (0.25 cycles/deg), which

may have depressed the contrast sensitivity at this particular spatial frequency. Calibration procedures followed those described in an earlier publication.²¹ The platform was placed at a greater distance from the stimuli than 57 cm in order to compensate for the amount the animal leaned prior to its leap. Monocular measurements were made of the contrast sensitivity for gratings of only one spatial frequency on each daily session. The measurement at this spatial frequency was repeated daily until identical thresholds were obtained on two successive sessions. Contrast threshold measurements then were made on the other eye for gratings of the same spatial frequency. It required 3 to 4 weeks to generate a contrast sensitivity function for the two eyes by this procedure.

Refractions

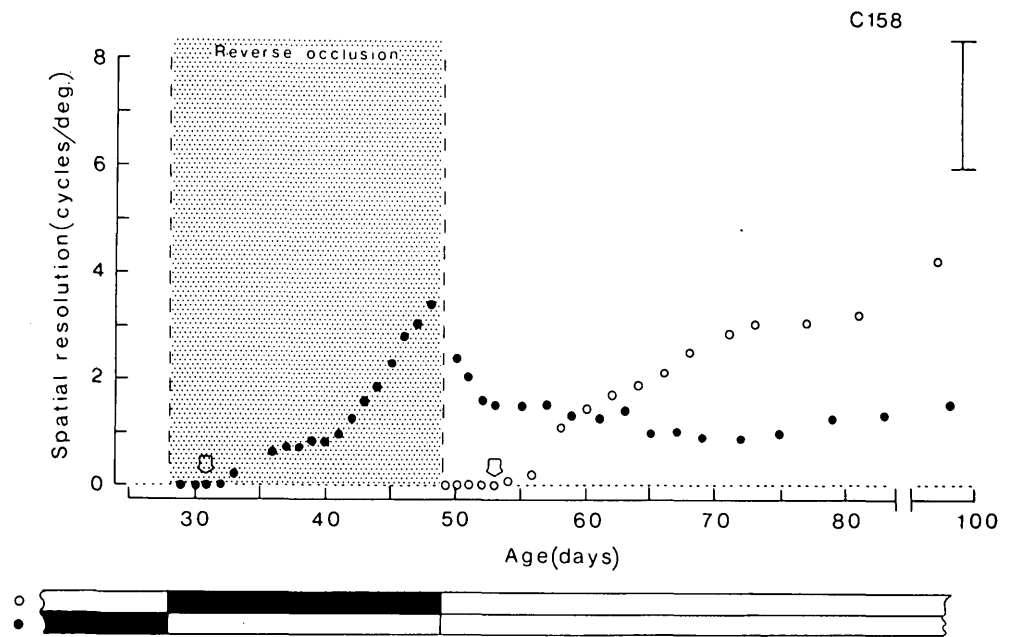
Cycloplegic retinoscopy was performed on all the kittens on conclusion of the behavioral tests. All eyes were within 1.0 D of emmetropia and interocular differences in refraction were negligible. None of these refractive errors could be expected to have significantly degraded visual performance.

The investigations on animals described herein conform to the ARVO Resolution on the Use of Animals in Research.

Results

The time course of recovery of vision in the deprived eye of two animals (C158 and C94) during the period of reverse occlusion (shaded region) are plotted in Figures 1 and 2 together with the changes that occurred afterwards to the vision of both eyes following restoration of binocular visual input. These results are representative of those obtained from animals from the two extreme rearing conditions. Figure 1 shows the results from an animal, C158, that was monocularly deprived until only 4 weeks of age and then reverse occluded for 3 weeks. Binocular visual input thus was introduced before it was 2-months-old at a time when neural connections in the visual cortex are still highly susceptible to environmental modification. By contrast, the data of Figure 2 are from an animal (C94) that was originally deprived for much longer (3 months) and reverse occluded for a similar time. Consequently, this animal was 6-months-old when binocular visual input was introduced. Both animals appeared to be blind when the initially deprived eye was first tested following reverse occlusion. The first signs of vision (defined by the ability to distinguish an open from a closed door on the jumping stand without obvious recourse to tactile or other cues) appeared on the third day in the case of C158 and after 16 days for C94. Pattern vision (the ability to distinguish a grating from a uniform field of the same mean luminance) usually

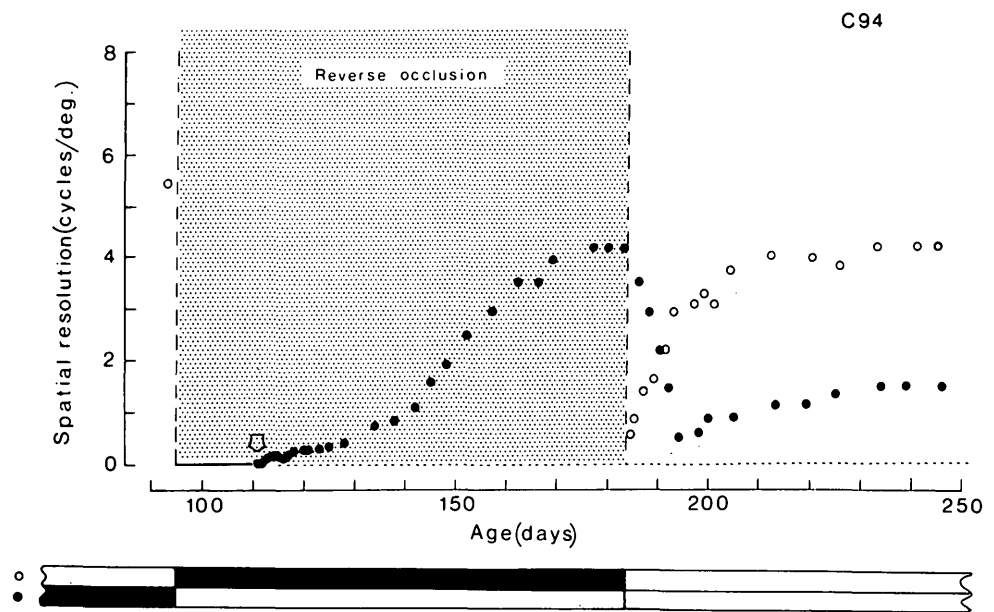
Fig. 1. The changes in the visual acuity of the deprived eye (●) of a monocularly deprived kitten (C158) during a period of reverse occlusion (shaded region), together with the changes that occur afterwards to the visual acuity of this eye as well as the initially nondeprived eye (○) upon restoration of binocular visual input. Reverse occlusion was imposed for 21 days at 28 days of age. The open arrow indicates the day on which the animal was first able to discriminate an open from a closed door on the jumping stand with its initially deprived eye. The vertical bar to the right depicts the range of acuities achieved by normal animals of comparable ages under similar testing conditions. The visual history of the animal is summarized below in schematic form.



appeared a day later after which the visual acuity showed gradual improvement. This increase in acuity occurred much faster with C158 than C94; the former achieved an acuity of 3.4 cycles/deg with its initially deprived eye after only 3 weeks of reverse occlusion, a level that was not reached by C94 for 2 months.

Despite the differences in the rate of recovery of vision of the initially deprived eye during reverse occlusion, the pattern of results obtained afterwards were remarkably similar. Upon restoration of binocular visual input, there was a rapid and reciprocal change in the visual acuity of the two eyes. Much of the sub-

Fig. 2. The changes in the visual acuity of the deprived eye (●) of a monocularly deprived kitten (C94) during an 89-day period of reverse occlusion (shaded region), together with the changes that occur afterwards to the visual acuity of this eye as well as the initially nondeprived eye (○) upon restoration of binocular visual input. The period of reverse occlusion was imposed at 94 days of age. Throughout the period of time indicated by the horizontal line, the animal appeared blind with its initially deprived eye. The open arrow indicates the day on which the animal was first able to discriminate an open from a closed door on the jumping stand with this eye. Note that prior to the period of reverse occlusion, the animal had attained an acuity of 5.45 cycles/deg with its initially nondeprived eye. The visual history of the animal is summarized below in schematic form.



prior to the period of reverse occlusion, the animal had attained an acuity of 5.45 cycles/deg with its initially nondeprived eye. The visual history of the animal is summarized below in schematic form.

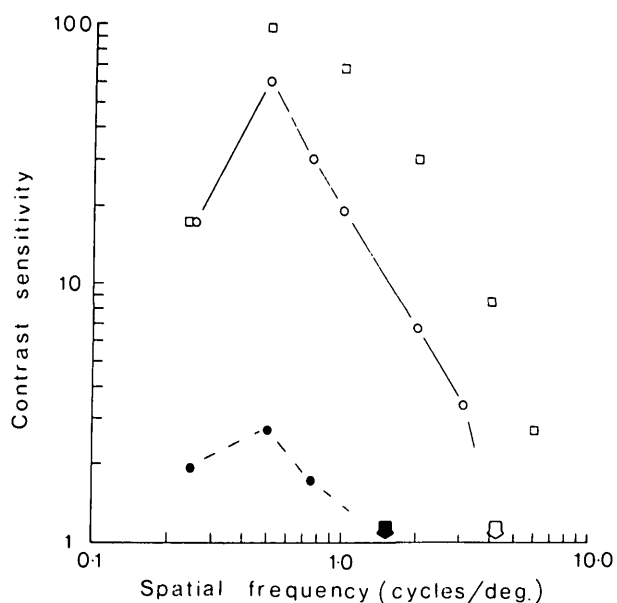


Fig. 3. Contrast sensitivity functions for the initially deprived (●) and nondeprived (○) eyes of C158 measured a month after completion of the last of the results shown in Figure 1. The open and filled arrows indicate the visual acuities of respectively, the initially nondeprived and deprived eyes measured with high contrast photographically reproduced square-wave gratings.

stantial gain in the vision of the initially deprived eye made during the period of reverse occlusion was lost within 2 or 3 weeks, while at the same time the vision of the initially nondeprived eye improved from the levels to which it had been depressed in this same period. The initial measurements of the visual acuity of the initially nondeprived eye made upon termination of reverse occlusion indicated that the dramatic improvements that occurred in the vision of the initially deprived eye during reverse occlusion were made at the expense of the vision of the other eye. This was particularly true for C158 who appeared blind for 3 days with the initially nondeprived eye following termination of reverse occlusion. The loss of vision in the initially nondeprived eye of C94 was not so profound; on initial testing following termination of reverse occlusion, it was obvious that the animal could see with this eye, although the acuity was reduced significantly to 0.5 cycles/deg. The acuity of the initially nondeprived eye of both animals improved rapidly but at a somewhat slower rate than the speed with which the acuity of the initially deprived eye dropped. The decline in the vision of the initially deprived eye was particularly fast in the week following termination of reverse occlusion and continued at a somewhat slower pace for a further 2 weeks with some slight improvement in the weeks that followed. On conclusion of behavioral testing after about 2 months, the acuity of the initially deprived eye of both animals was only 1.5

cycles/deg, while that of the other eye had improved to just over 4 cycles/deg.

In the case of C94, the acuity that eventually was attained by the initially nondeprived eye following restoration of binocular visual input was comparable to the acuity of the deprived eye at the end of the period of reverse occlusion. However, at the same time it was significantly lower than the value it had attained previously (5.45 cycles/deg), during the initial period of monocular deprivation. A somewhat similar result was apparent with C158. The final measured acuity of the initially nondeprived eye 2 months after termination of reverse occlusion (4.25 cycles/deg), while certainly better than the acuity that this eye would have attained prior to reverse occlusion, was, nevertheless, substantially lower than the acuity of normal animals (6.0 to 8.4 cycles/deg under the experimental conditions employed here). Thus, neither animal regained normal vision with their initially nondeprived eye following termination of reverse occlusion.

Measurements of the contrast sensitivity functions of the two eyes of C158 made 4 to 6 weeks after completion of the longitudinal acuity measurements of Figure 1 revealed differences between the two eyes that were even more striking than those evident in their visual acuities. The results of these measurements made with the initially deprived and nondeprived eyes are shown in Figure 3 by filled and open circles, respectively. The open and filled arrows depict the final visual acuity measurements of Figure 1 made with photographically reproduced square-wave gratings at a luminance level that was virtually identical to that employed for the measurements of contrast sensitivity. The good agreement between these values and the cut-off spatial frequency extrapolated from the contrast sensitivity function for the two eyes point to the internal consistency between these two measurements. The open square symbols show the results of monocular measurements made on a normally reared adolescent cat of a similar age. These contrast sensitivities are closely similar to those reported for normal animals in previous investigations²²⁻²⁴ that employed alternative sensitive procedures. They also highlight the fact that the contrast sensitivities of the initially nondeprived eye of the former were subnormal at all but the lowest spatial frequencies. The deficits in contrast sensitivity of the initially deprived eye were extremely profound at all spatial frequencies. At 0.5 cycle/deg, where sensitivity was highest for both eyes, the contrast sensitivity of the initially nondeprived eye was more than 20 times better than that of the initially deprived eye.

Reciprocal changes in visual acuity were observed in all animals upon termination of reverse occlusion. Results from the three remaining animals that initially

were deprived for short periods (to 5, 6, and 9.5 weeks) are shown in Figure 4. For economy, only the changes in visual acuity that occurred following termination of reverse occlusion are shown. In each case, the first filled symbol indicates the visual acuity of the initially deprived eye at the end of the period of reverse occlusion. Despite the fact that the initially deprived eye had attained an acuity in excess of 5 cycles/deg during this period for all three animals, upon restoration of visual input to both eyes, the acuity of this eye dropped rapidly. This was particularly true for the initially deprived eye of C136 which dropped from 5.7 cycles/deg to 0.4 cycles/deg in only 3 weeks! The drop in the acuity of the initially deprived eye of C141 (from 5.2 to 1.4 cycles/deg) was not quite so dramatic, while the reduction observed with C115 was comparatively small. The decline in the acuity of the formerly deprived eye of all three animals was accompanied by an improvement in the vision of the other eye that was just as remarkable. Both C141 and C136 at first appeared blind with their initially nondeprived eye following the period of reverse occlusion, yet within 3 to 4 weeks the vision of this eye recovered to approach the lower end of the range encountered in normal animals.

Results from three animals that were reverse occluded late, at 3 to 3.5 months of age, are displayed in Figure 5. The horizontal lines indicate the acuity of the nondeprived eye at the end of the initial period of monocular deprivation. By the end of the 3-month period of reverse occlusion the visual acuity of the initially deprived eye had recovered to about 4 cycles/deg. But, as with the other animals, on restoration of binocular visual input the vision of this eye declined rapidly. In one case (C124), the vision of this eye fell to such an extent that the animal was only capable of discriminating an open from a closed door on the jumping stand when using this eye. As with the animals of Figure 4, the vision of the initially nondeprived eye fell substantially during the long period of reverse occlusion. However, in contrast to most of the animals that were reverse occluded early in life, this eye was not rendered blind by this procedure. On restoration of binocular visual input, the vision of this eye improved rapidly to approximately the level that had been reached by the initially deprived eye during reverse occlusion. However, in no animal did the acuity of the initially nondeprived eye recover to the normal levels that it had once reached during the early period of monocular deprivation.

Reciprocal changes in visual acuity as rapid as those described above also were observed in the animal (C137) that initially was deprived the longest, to 135 days of age. The gradual recovery of vision of the initially deprived eye during 2 months of reverse occlusion

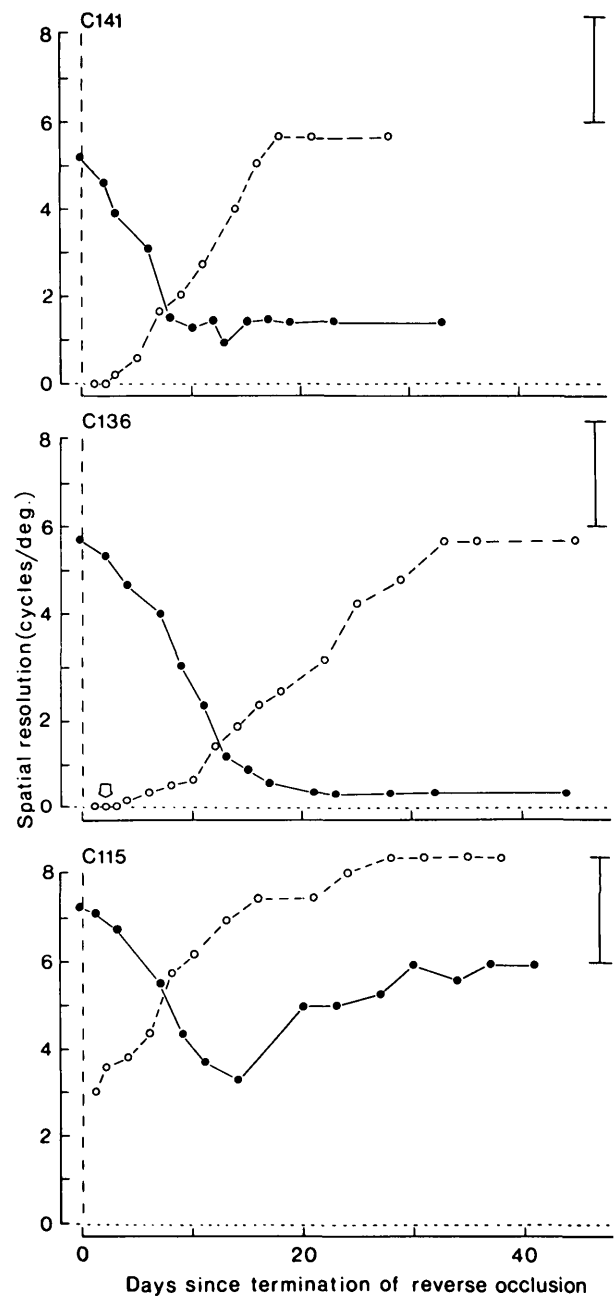


Fig. 4. Changes in the visual acuities of the initially deprived (●) and nondeprived (○) eyes of three monocularly deprived kittens (C141, C136, and C115) following termination of reverse occlusion and introduction of binocular visual input. The vertical bars to the right depict the range of acuities achieved by normal animals. The individual deprivation conditions were as follows. C141: reverse occlusion for 38 days imposed at 35 days of age; C136: reverse occlusion for 44 days imposed at 41 days of age; C115: reverse occlusion for 35 days imposed at 66 days of age.

as well as the changes that occurred subsequently to the acuity of both eyes are shown in Figure 6. As with the animals of Figure 5, on termination of reverse occlusion, the visual acuity of the formerly nondeprived eye rose only to about the level that had been reached

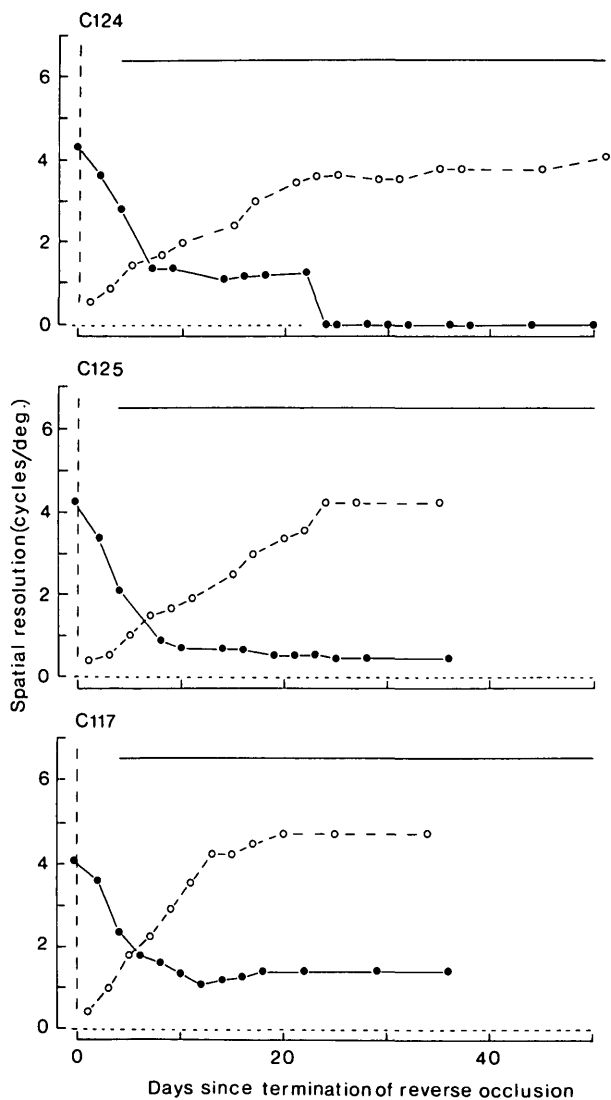


Fig. 5. Changes in the visual acuities of the initially deprived (●) and nondeprived (○) eyes of three monocularly deprived kittens (C124, C125, and C117) following termination of reverse occlusion and introduction of binocular visual input. The long horizontal bar at the top of each graph indicates the acuity of the initially nondeprived eye at the end of the initial period of monocular deprivation. The individual deprivation conditions were as follows. C124: reverse occlusion for 88 days imposed at 94 days; C125: reverse occlusion for 102 days imposed at 101 days; C117: reverse occlusion for 91 days imposed at 103 days.

by the initially deprived eye at the end of the period of reverse occlusion. Consequently, the acuity of this eye at the conclusion of testing (2.75 cycles/deg) was much lower than the level it had reached (6.4 cycles/deg) earlier during the initial period of monocular deprivation.

Discussion

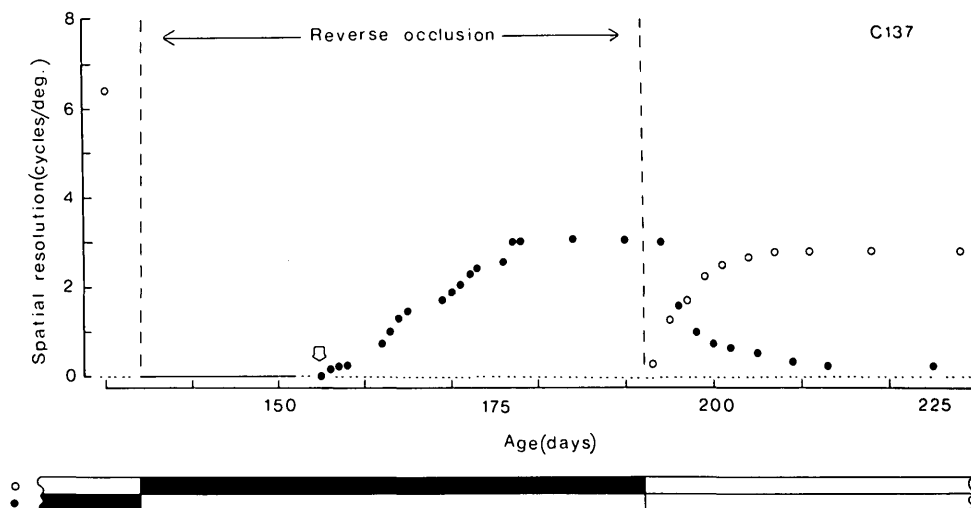
In agreement with earlier results,⁷ the vision of the deprived eye of monocularly deprived kittens was im-

proved substantially by a period of reverse occlusion. When reverse occlusion was implemented early, as was the case for C158, C141, C136, and C115, the acuity of the deprived eye recovered to levels comparable with those of normal animals of the same age.

Nevertheless, most of the impressive gain in vision was lost rapidly upon restoration of binocular visual input. At the same time, the vision of the initially nondeprived eye rose rapidly from the levels to which it had been depressed during the period of reverse occlusion. Of the reciprocal changes in acuity that occurred following termination of reverse occlusion, the rapid decline in the vision of the formerly deprived eye was the most surprising. This was especially true of animals such as C158, C141, and C136, which were reverse occluded early for periods of time that are known to either produce a complete shift of ocular dominance of visual cortical cells towards the formerly deprived eye (C158 and C141), or else the maximum shift of ocular allegiance possible at that particular age (C136).²⁵ Because the magnitude of the shifts in cortical ocular dominance in these circumstances are as dramatic as those observed following an early period of monocular deprivation, it might be thought that the behavioral and physiologic events that followed restoration of binocular visual input would be similar to those observed on restoring binocular visual input following a period of monocular deprivation. In the latter situation, the vision of the deprived eye gradually improves without concurrent deterioration of the vision of the other eye.^{7,14} An example of recovery in this situation, obtained from a littermate of C124 and C125 that was monocularly deprived for an identical period to C124 (to 94 days of age), is shown in Figure 7. The deprived eye remained apparently blind for 18 days after which it improved gradually to 3.35 cycles/deg during the next month. In contrast to the results obtained following termination of reverse occlusion, the gain in the vision of the previously occluded eye was not at the expense of the vision of the other eye, which remained at normal levels throughout the time that the vision of the deprived eye improved.

While the nature and extent of the physiologic changes that occur in the visual cortex following termination of reverse occlusion are still under investigation (Murphy, Cynader, and Mitchell, in preparation), a number of conclusions and predictions can be made on the basis of the behavioral results. One major implication of these findings is that some of the striking shifts of ocular allegiance of cortical cells that occur during reverse occlusion may not be permanent. In cases where reverse occlusion was initiated at 4, 5, or 6 weeks of age, large shifts of cortical ocular dominance have been reported.²⁵ Nevertheless, the rapid behav-

Fig. 6. The changes in the visual acuity of the initially deprived eye (●) of a monocularly deprived cat (C137) during 58 days of reverse occlusion imposed at 134 days of age, together with the changes that occur afterwards to the vision of this eye as well as to that of the initially nondeprived eye (○) upon restoration of binocular visual input. Throughout the period indicated by the horizontal line, the animal appeared blind with its initially deprived eye. The first sign of vision with this eye (the ability to discriminate an open from a closed door on the jumping stand) is indicated by the open arrow. Note that prior to the period of reverse occlusion, the acuity of the initially nondeprived eye was 6.4 cycles/deg. The visual history of the animal is depicted below in schematic form.



Throughout the period indicated by the horizontal line, the animal appeared blind with its initially deprived eye. The first sign of vision with this eye (the ability to discriminate an open from a closed door on the jumping stand) is indicated by the open arrow. Note that prior to the period of reverse occlusion, the acuity of the initially nondeprived eye was 6.4 cycles/deg. The visual history of the animal is depicted below in schematic form.

ioral changes that are observed afterwards suggest that some of the physiologic events that occur during reverse occlusion are, themselves, quickly reversed. The behavioral changes reported here also hold important implications for the nature of the mechanisms that underlie the shifts of cortical ocular dominance during reverse occlusion. The behavioral data suggest that the mechanism responsible for the shifts of cortical ocular dominance that take place during reverse occlusion must be in some way different from that responsible for the shifts that occur during the initial period of monocular deprivation. This conclusion is particularly persuasive for those animals that were reverse occluded at 4 or 5 weeks of age for periods that were sufficiently long to produce a shift of cortical ocular dominance toward the initially deprived eye as biased as that observed toward the nondeprived eye at the end of a comparable period of monocular deprivation. Despite the similar magnitude of the physiologic effects of these two deprivation conditions on the visual cortex, the consequences for vision upon restoration of binocular visual input are quite different.

There are a number of plausible explanations for these different results. One remote possibility is that the reciprocal changes in vision observed following reverse occlusion are, in part, an artifact resulting from a misalignment of the visual axes. According to this notion, the rapid loss of vision of the initially deprived eye observed on restoring visual input to both eyes represents the rapid onset of strabismic amblyopia in this eye. This explanation must be considered extremely unlikely for several reasons. First, it does not account for the different behavioral outcome when

vision is restored to both eyes after monocular deprivation. And second, it requires that the visual axes have a convergent misalignment since strabismic amblyopia rarely is observed otherwise.^{26,27} Only two of our animals exhibited a possible esotropia on casual inspection (C115 and C141), and the only one on which quantitative measurements were made (C136) had normal eye alignment. Finally, the time course of the visual changes as well as the ages at which they occur

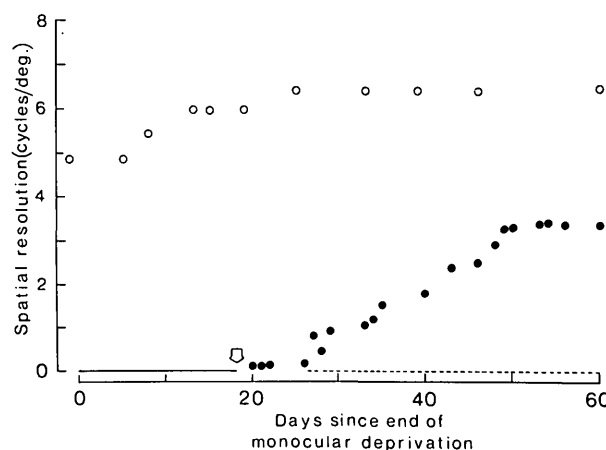


Fig. 7. The recovery of vision in the deprived eye (●) of a monocularly deprived cat on restoration of binocular visual input. This particular animal was deprived from the time of eye opening until 94 days of age. The visual acuities of the nondeprived eye (○) during the recovery period are also shown. Throughout the period indicated by the horizontal line, the animal appeared blind with its deprived eye. Note that in contrast to the effects observed on termination of reverse occlusion, the recovery of vision in the deprived eye was not at the expense of the vision of the nondeprived eye.

(as late as 6 months of age), are both very different from what might be expected on the basis of current knowledge of experimentally induced strabismus in cats. The onset of strabismic amblyopia is comparatively slow²³ and apparently only occurs if esotropia is induced before the third month of life.²⁸

Alternatively, it is possible that the different behavioral outcomes may be explained in terms of differences in the effects of monocular occlusion on layer IV of the visual cortex. During the early period of monocular deprivation, there is opportunity for the process of segregation of geniculocortical afferents from the two eyes in layer IV to be altered by the discordant nature or the visual input from the two eyes.²⁹ On the other hand, the period of reverse occlusion was imposed comparatively late at a time when segregation of afferents from the two eyes in layer IV is almost complete.³⁰ Although by analogy with the monkey,⁴ it is possible that some further changes may be induced in layer IV by reverse occlusion imposed somewhat beyond the time when segregation is normally complete, any such changes would be expected to be small. Nevertheless, it could be argued that the different behavioral effects observed on termination of reverse occlusion as opposed to an early period of monocular deprivation, simply reflects the differences in the magnitude of their effects on layer IV. However, it is unlikely that the different behavioral outcomes could be accounted for solely in such terms since the behavioral effects observed on termination of a period of monocular occlusion are no different even if applied at 2 or 3 months of age at a time when segregation of geniculocortical afferents in layer IV is complete.⁷

A somewhat more compelling set of possibilities suggest themselves on the basis of the speed and nature of the visual changes that occur on termination of reverse occlusion. Not only were these changes rapid (especially the fall in the acuity of the deprived eye), but they were also remarkably similar in time course no matter at what age reverse occlusion was terminated. This raises the possibility that some of the changes in cortical ocular allegiance that occur in the visual cortex during reverse occlusion may be mediated by a process of "tonic inhibition"³¹ or "synaptic suppression."³³ The first of these mechanisms proposes that synaptic connections from the initially nondeprived eye are rendered ineffective during reverse occlusion by a process of active inhibition by activity in the pathway from the formerly deprived eye. The second mechanism postulates that the efficacy of synaptic transmission in the pathway from the initially nondeprived eye is in some way reduced. While these processes may take some time to develop, there is some evidence to suggest that they might be reversed quickly.³¹⁻³³ The

fact that the visual changes on termination of reverse occlusion occurred at a similar rate no matter at what age they occurred would seem consistent with mechanisms of this nature.

Clinical Implications

The procedure of reverse occlusion following early monocular deprivation is analogous to the clinical procedure of patching for treatment of amblyopia. It is, therefore, of interest that similar reciprocal changes in visual acuity to those reported here have been observed following termination of patching therapy of young human infants with severe amblyopia.³⁴⁻³⁷ Discovery of a similar phenomenon in kittens not only allows investigation of the underlying anatomic and physiologic mechanisms but also permits a systematic search for optimum treatment regimens. As a first step toward such a goal we have begun (Murphy and Mitchell, in preparation) a systematic survey of the consequences for vision of periods of reverse occlusion of various durations imposed on kittens that were monocularly deprived until 4, 5, or 6 weeks of age.

A second interesting feature of the results reported here was the substantial effect of reverse occlusion on the vision of the formerly nondeprived eye. In many cases, this eye was even rendered temporarily blind by this procedure. While the vision of this eye improved subsequently, in some cases to approach normal levels, in many instances the acuity of this eye never recovered to levels it had attained prior to the period of reverse occlusion. This was particularly noteworthy for those animals that were reverse occluded late and for long periods (C94, C124, C125, C117, and C137). In certain respects then, the eventual benefits of reverse occlusion could be considered somewhat dubious. Not only was the vision of the formerly nondeprived eye permanently depressed, but the vision of the formerly deprived eye was only marginally better than it was prior to reverse occlusion! The reduction in the vision of the initially nondeprived eye by reverse occlusion could be considered an exaggeration of the clinical condition of 'occlusion amblyopia' that is sometimes observed following prolonged patching therapy of human amblyopes.³⁸ The findings of this study, thus, reinforce the use of current treatment strategies for deprivation (and other) amblyopia that require patching for only a part of each day in order to prevent the onset of occlusion amblyopia.^{8,9,34,35,38-40} At the same time, it is possible that such procedures also may allow the recovery promoted by the daily periods of patching to be sustained.

Key words: amblyopia, deprivation, visual acuity, patching therapy, reverse occlusion, cats

Acknowledgments

The authors wish to thank Cindy Trask and Heather Dzioba for their dedicated care of the animals and their assistance with some of the behavioral measurements.

References

1. Mitchell DE and Timney B: Postnatal development of function in the mammalian visual system. *In Handbook of Physiology, Section I: The Nervous System, Vol 3, Sensory Processes, Part 1, Darian-Smith I, editor. Bethesda, American Physiological Society, 1984, pp. 507-555.*
2. Movshon JA and Van Sluyters RC: Visual neuronal development. *Ann Rev Psychol* 32:477, 1981.
3. Wiesel TN and Hubel DH: Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J Neurophysiol* 26:1003, 1963.
4. LeVay S, Wiesel TN, and Hubel DH: The development of ocular dominance columns in normal and visually deprived monkeys. *J Comp Neurol* 191:1, 1980.
5. Hubel DH, Wiesel TN, and LeVay S: Plasticity of ocular dominance columns in monkey striate cortex. *Phil Trans R Soc Lond B* 278:377, 1977.
6. Dews PB and Wiesel TN: Consequences of monocular deprivation on visual behaviour in kittens. *J Physiol* 206:437, 1970.
7. Giffin F and Mitchell DE: The rate of recovery of vision after early monocular deprivation in kittens. *J Physiol* 274:511, 1978.
8. von Noorden GK: Experimental amblyopia in monkeys. Further behavioral observations and clinical correlations. *Invest Ophthalmol* 12:721, 1973.
9. von Noorden GK: New clinical aspects of stimulus deprivation amblyopia. *Am J Ophthalmol* 92:416, 1981.
10. Vaegan and Taylor D: Critical period for deprivation amblyopia in children. *Trans Ophthalmol Soc UK* 99:432, 1980.
11. Hess RT, France T, and Tulanay-Keesey U: Residual vision in humans who have been monocularly deprived of pattern stimulation in early life. *Exp Brain Res* 44:295, 1981.
12. von Noorden GK: Classification of amblyopia. *Am J Ophthalmol* 63:238, 1967.
13. Blakemore C and Van Sluyters RC: Reversal of the physiological effects of monocular deprivation in kittens: further evidence for a sensitive period. *J Physiol* 237:195, 1974.
14. Mitchell DE, Cynader M, and Movshon JA: Recovery from the effects of monocular deprivation in kittens. *J Comp Neurol* 176:53, 1977.
15. Harwerth RS, Crawford MLJ, Smith EL, and Bolz RL: Behavioral studies of stimulus deprivation amblyopia in monkeys. *Vision Res* 21:779, 1981.
16. Blakemore C, Vital-Durand F, and Garey LJ: Recovery from monocular deprivation in the monkey. I. Reversal of physiological effects in the visual cortex. *Proc R Soc Lond B* 213:399, 1981.
17. Blakemore C, Garey LJ, and Vital-Durand F: The physiological effects of monocular deprivation and their reversal in the monkey's visual cortex. *J Physiol* 283:223, 1978.
18. Mitchell DE, Murphy KM, and Kaye MG: Labile nature of the visual recovery promoted by reverse occlusion in monocularly deprived kittens. *Proc Natl Acad Sci USA* 81:286, 1984.
19. Mitchell DE, Giffin F, and Timney B: A behavioural technique for the rapid assessment of the visual capabilities of kittens. *Perception* 6:181, 1977.
20. Mitchell DE and Timney B: Behavioural measurement of normal and abnormal development of vision in kittens. *In Analysis of Visual Behavior, Ingle D, Goodale MA, and Mansfield RJW, editors. Cambridge, MIT Press, 1982, pp. 483-523.*
21. Mitchell DE and Wilkinson F: The effect of early astigmatism on the visual resolution of gratings. *J Physiol* 243:739, 1974.
22. Blake R, Cool SJ, and Crawford MLJ: Visual resolution in the cat. *Vision Res* 14:1211, 1974.
23. Bisti S and Maffei L: Behavioural contrast sensitivity of the cat in various visual meridians. *J Physiol* 241:201, 1974.
24. Campbell FW, Maffei L, and Piccolino M: The contrast sensitivity of the cat. *J Physiol* 229:719, 1973.
25. Movshon JA: Reversal of the physiological effects of monocular deprivation in the kitten's visual cortex. *J Physiol* 261:125, 1976.
26. Freeman RD, Sclar G, and Ohzawa I: An electrophysiological comparison of convergent and divergent strabismus in the cat: visual evoked potentials. *J Neurophysiol* 49:227, 1983.
27. Kaye M, Mitchell DE, and Ruck M: Immediate and long-term effects on visual acuity of surgically induced strabismus in kittens. *ARVO Abstracts. Invest Ophthalmol Vis Sci* 24(Suppl):22, 1983.
28. Jacobson SG and Ikeda H: Behavioural studies of spatial vision in cats reared with convergent squint: is amblyopia due to arrest of development? *Exp Brain Res* 34:11, 1979.
29. Shatz CJ and Stryker MP: Ocular dominance in layer IV of the cat's visual cortex and the effects of monocular deprivation. *J Physiol* 281:267, 1978.
30. LeVay S, Stryker MP, and Shatz CJ: Ocular dominance columns and their development in layer IV of the cat's visual cortex: a quantitative study. *J Comp Neurol* 179:223, 1978.
31. Kratz KE, Spear PD, and Smith DC: Post-critical period reversal of effects of monocular deprivation on the striate cortex in cats. *J Neurophysiol* 39:501, 1976.
32. Blakemore C and Hawken MJ: Rapid restoration of functional input to the visual cortex of the cat after brief monocular deprivation. *J Physiol* 327:463, 1982.
33. Blakemore C, Hawken MJ, and Mark RF: Brief monocular deprivation leaves subthreshold synaptic input on neurones of the cat's visual cortex. *J Physiol* 327:489, 1982.
34. Jacobson SG, Mohindra I, and Held R: Development of visual acuity in infants with congenital cataracts. *Br J Ophthalmol* 65:727, 1981.
35. Jacobson SG, Mohindra I, and Held R: Monocular visual form deprivation in human infants. *Doc Ophthalmol* 55:199, 1983.
36. Odom JV, Hoyt CS, and Marg E: Effect of natural deprivation and unilateral eye patching on visual acuity of infants and children. *Arch Ophthalmol* 99:1412, 1981.
37. Marg E: Is the animal model for stimulus deprivation amblyopia in children valid or useful? *Am J Optom Physiol Opt* 59:451, 1982.
38. Duke-Elder S and Wybar K: Ocular motility and strabismus. *In System of Ophthalmology, Vol 6, Duke-Elder S, editor. London, Kimpton, 1973, pp. 295, 424-432.*
39. Enoch JM and Rabinowicz IM: Early surgery and visual correction of an infant born with unilateral eye lens opacity. *Doc Ophthalmol* 41:371, 1976.
40. Beller R, Hoyt CS, Marg E, and Odom JV: Good visual function after neonatal surgery for congenital monocular cataracts. *Am J Ophthalmol* 91:559, 1981.