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# The Long-Term Effectiveness of Different Regimens of Occlusion on Recovery from Early Monocular Deprivation in Kittens

Donald E. Mitchell

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# The long-term effectiveness of different regimens of occlusion on recovery from early monocular deprivation in kittens

DONALD E. MITCHELL

*Psychology Department, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J1*

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## SUMMARY

Although the behavioural effects of an early period of monocular deprivation imposed on kittens can be very severe, resembling an extreme form of the human clinical condition deprivation amblyopia, they are not necessarily irreversible. Considerable behavioural as well as physiological recovery can occur if normal visual input is restored to the deprived eye sufficiently early, particularly if the other (initially non-deprived) eye is occluded at the same time (reverse occlusion). However, past work has shown that in many situations the improvement in the vision of the initially deprived eye that occurs during reverse occlusion is not retained following the subsequent introduction of binocular visual input. Furthermore, the vision of the other eye is often reduced as well, with the result that the eventual outcome is a condition of bilateral amblyopia. This study first examines the consequences of several periods of reverse occlusion whose onset and duration would be thought to maximize the opportunity for good and long-standing recovery of vision in the initially deprived eye. However, only in a very restricted set of exposure conditions did animals acquire good vision in one or both eyes; in most situations the final outcome was one of bilateral amblyopia.

A second set of experiments examined the consequences of various regimens of part-time reverse occlusion, where the initially non-deprived eye was occluded for only part of each day to allow a period of binocular visual exposure, on kittens that had been monocularly deprived until 6, 8, 10 or 12 weeks of age. Whereas short or long daily periods of occlusion of the initially non-deprived eye resulted eventually in amblyopia in one, or usually both, eyes, certain intermediate occlusion times (3.5 or 5 h each day) resulted in recovery of normal acuities, contrast sensitivity and vernier acuity in both eyes, in animals that had been monocularly deprived until 6, 8 or 10 weeks of age, but not in animals deprived for longer periods. Experiments were done to establish some of the factors that contributed to the successful outcome associated with certain of the regimens of part-time reverse occlusion. It was established that recovery was just as good in animals in which the visual axes were vertically misaligned by means of prisms during the daily period of binocular visual exposure, thereby indicating that the visual input to the two eyes need not be concordant. However, animals that received equivalent visual exposure of the two eyes each day, but successively rather than simultaneously, all developed very severe bilateral amblyopia. It would

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appear that for recovery to occur it is necessary for the two eyes to receive simultaneous, but not necessarily concordant, visual exposure. These findings hold important implications for the nature of the mechanisms responsible for the dramatic behavioural changes associated with monocular deprivation and reverse occlusion, and for the clinical treatment of various forms of amblyopia in human infants.

## 1. INTRODUCTION

For some time it has been known that the severe initial behavioural effects of early monocular deprivation in kittens are not necessarily permanent, as considerable and rapid improvement of the vision of the deprived eye can occur if normal visual input is provided to this eye sufficiently early in life (Dews & Wiesel 1970; Movshon 1976*b*; Mitchell *et al.* 1977*a*; Giffin & Mitchell 1978; Mitchell 1988). However, if the deprivation is extended to about one year of age the deprived eye subsequently recovers little or no measurable vision (Berkley 1981; Smith & Holdefer 1985; Mitchell 1988). The initial behavioural deficits that follow monocular deprivation are presumed to be a consequence of the very substantial changes of ocular dominance and reduced binocular interactions induced among cells in the visual cortex by this form of deprivation (Movshon & Van Sluyters 1981; Mitchell & Timney 1984). Similarly, the behavioural recovery observed upon restoration of normal visual input to the deprived eye is mirrored by rapid and substantial shifts of ocular dominance in the visual cortex toward the deprived eye (Mitchell *et al.* 1977*a*; Olson & Freeman 1978*a*). The extent of these physiological changes is accentuated when the formerly non-deprived eye is occluded at the same time that normal visual input is provided to the deprived eye, a procedure referred to as reverse occlusion (Blakemore & Van Sluyters 1974; Movshon 1976*a*). Reverse occlusion also produces a similar enhancement of behavioural recovery, which is particularly evident following relatively short periods of monocular deprivation that extend to eight weeks of age or less (Mitchell 1988). Considerable and rapid physiological and behavioural recovery have also been reported in monocularly deprived monkeys following reverse occlusion (Blakemore *et al.* 1978, 1981; LeVay *et al.* 1980; Harwerth *et al.* 1989; Crawford *et al.* 1989). However, in this species little or no anatomical and physiological recovery occurs in the passive situation where both eyes are open following the initial period of monocular deprivation (Baker *et al.* 1974; Hubel *et al.* 1977; Blakemore *et al.* 1981; Swindale *et al.* 1981).

Recently it has been demonstrated that the beneficial behavioural effects of a period of reverse occlusion on monocularly deprived kittens may be evident only during the time it is imposed, as the vision of the initially deprived eye can deteriorate rapidly after simultaneous visual input is provided to both eyes (Mitchell *et al.* 1984*a*, *b*). Moreover, not only can the vision of the initially deprived eye sometimes decline in a dramatic fashion during the latter period, but the vision of the recently opened (initially non-deprived) eye may recover only limited vision, leading eventually to a situation of bilateral amblyopia in which the vision of both eyes is poor (Murphy & Mitchell 1986, 1987). Very surprisingly, the latter outcome has been reported in two situations that might be thought to provide optimal conditions for long-standing recovery of the vision of the initially deprived eye. These include situations in which reverse occlusion was introduced early for either very brief periods, so that the animal received binocular visual exposure while it was still very young (five to seven weeks of age), or else for protracted periods of two to three months. The severity and frequency of bilateral amblyopia led to the exploration of the effectiveness of various regimens of part-time reverse occlusion whereby the initially non-deprived eye was occluded for only part of each day, allowing for a daily period during which both eyes were open simultaneously. In an earlier brief report on kittens that had been monocularly deprived to six weeks of age (Mitchell *et al.* 1986), a successful regimen of part-time reverse occlusion was described that produced long-term recovery of the vision of the initially deprived eye without inducing any deleterious effects on the vision of the other eye. Upon opening the eyelids of the initially deprived eye, the animals were allowed only seven hours of daily visual exposure, during which time the initially non-deprived eye of each animal was covered by an opaque mask for various periods of from 1 to 7 h. For the remaining period of daily visual exposure the mask was removed to allow simultaneous visual input to both eyes. The animals that received either 3.5 (50% part-time occlusion) or five (70% part-time occlusion) hours of part-time reverse occlusion in this manner eventually recovered normal visual acuities in both eyes.

Subsequent to the work described above, the eventual consequences of a wide variety of different regimens of both full-time and part-time reverse occlusion have been examined in an attempt to establish those exposure conditions that optimize the recovery of vision in both eyes. One of the prime motives for this undertaking was to establish guidelines that could be useful for optimizing occlusion treatment of human amblyopia. However, beyond these clinical concerns was the additional idea that such parametric studies might provide important insights into the mechanisms that lead to such surprising and complex behavioural events following different regimens of reverse occlusion.

The results of these additional studies of the long-term effects of various regimens of full-time and part-time reverse occlusion are described below. The new studies of full-time reverse occlusion were designed to delineate the conditions that result in bilateral amblyopia as well as to explore further those occlusion parameters that would be thought to allow the vision recovered by the deprived eye during the period of reverse occlusion to be maintained afterwards. The studies of part-time reverse occlusion examined the effectiveness of this procedure when imposed on animals that had been monocularly deprived from

Table 1. *Rearing histories and final visual acuities of 22 monocularly deprived kittens that subsequently received full-time reverse occlusion*

(With the exception of C214 and C218, the kittens were monocularly deprived from near the time of natural eye-opening until the various ages shown when a period of reverse occlusion of the duration indicated was imposed.)

| | reverse occlusion | | eventual visual acuity (cycles deg$^{-1}$) | |
|---|---|---|---|---|
| cat | imposed at (days of age) | duration (days) | initially deprived eye | initially non-deprived eye |
| C162[a] | 21 | 14 | 2.75 | 3.20 |
| C392[a] | 25 | 84 | 7.75 | 0.85 |
| C379[a] | 28 | 111 | 7.60 | 0.60 |
| C377[a] | 29 | 140 | 8.20 | 0.80 |
| C378[a] | 29 | 168 | 8.20 | 1.25 |
| C285 | 35 | 35 | 1.80 | 5.90 |
| C286 | 35 | 35 | 1.90 | 6.15 |
| C362 | 35 | 84 | 0.42 | 5.50 |
| C401 | 35 | 84 | 1.15 | 1.35 |
| C427 | 36 | 9 | 1.80 | 2.10 |
| C175 | 39 | 39 | 2.32 | 5.39 |
| C404 | 41 | 43 | 2.80 | 7.50 |
| C405 | 41 | 43 | 3.50 | 7.50 |
| C415 | 41 | 43 | 2.15 | 7.05 |
| C416 | 41 | 44 | 3.40 | 7.00 |
| C429 | 42 | 42 | 3.30 | 7.45 |
| C428 | 42 | 42 | 4.45 | 7.60 |
| C204 | 64 | 35 | 5.04 | 6.10 |
| C107[a] | 89 | 56 | 3.50 | 2.20 |
| C190[a] | 141 | 89 | 1.90 | 2.40 |
| C214[a, b] | 49 | 43 | 3.30 | 3.30 |
| C218[a, b] | 60 | 39 | 3.95 | 3.55 |

[a] Animals with rearing histories different from those described in previous papers.

[b] Animals that received normal visual input until either 28 (C214) or 36 (C218) days of age before the initial period of monocular deprivation.

near birth to 6, 8, 10 or 12 weeks of age. In addition, experiments were done to try to identify those features of this latter procedure that are crucial to its success in certain situations.

## 2. METHODS

### (*a*) *Animals and rearing conditions*

The effects of a variety of different regimens of full-time or part-time reverse occlusion were studied on a total of 92 monocularly deprived kittens that were bred and raised in a closed laboratory colony. Certain aspects of the findings from 29 of the 51 animals that received full-time reverse occlusion are highlighted in earlier papers (Mitchell *et al.* 1984*a*, *b*; Murphy & Mitchell 1987). Thirteen of the remaining 22 kittens that received full-time reverse occlusion were reared primarily for related and as yet unpublished anatomical or physiological studies and represented duplication of certain key rearing regimens examined in earlier behavioural studies. The remaining nine animals that received full-time reverse occlusion were reared specifically for this study. Table 1 lists the rearing histories as well as the final visual acuities of the two eyes of the 22 full-time reverse occluded animals that are described here for the first time.

Of the 41 animals that received various regimens of part-time reverse occlusion of one or both eyes, 24 were reared for the purpose of parametric study of the effects of different daily regimens of part-time occlusion of the non-deprived eye when imposed on kittens that had been monocularly deprived to 6, 8, 10 or 12 weeks of age. Table 2 lists the rearing histories of these 24 animals together with the final visual acuities that were attained in the two eyes. The remaining 17 animals were used for studies that examined either the factors that contributed to the success of certain of these procedures or the effects of different regimens of full-time followed by part-time reverse occlusion. The rearing histories of these particular animals are summarized in table 3.

The eyelids of one eye of each kitten were sutured closed at about the time of natural eye-opening when the animals were from 4 to 11 days old. Eyelid closure was done under halothane anaesthesia by use of a surgical procedure that has been described in detail elsewhere (Murphy & Mitchell 1987) and which maintains the integrity of the lid margins. When the animals were from 21 to 141 days old the initial period of monocular eyelid closure was terminated by parting the closed eyelids of the deprived eye under halothane anaesthesia. Because the procedures employed for the

Table 2. *Rearing histories and final visual acuities of 24 monocularly deprived kittens that subsequently received various regimens of part-time reverse occlusion*

(The animals were monocularly deprived from near the time of natural eye-opening until the various ages shown, when a period of part-time reverse occlusion of the duration indicated was imposed. During the latter period the animals received only 7 h of daily visual exposure. Each day the initially non-deprived eye was occluded for the time indicated. For C327 this eye was either occluded for all 7 h of the day or not at all on an alternating basis.)

| | part-time reverse occlusion | | | eventual visual acuity (cycles deg$^{-1}$) | |
|---|---|---|---|---|---|
| cat | imposed at (days of age) | duration (days) | hours each day | initially deprived eye | initially non-deprived eye |
| C229 | 42 | — | 0 | 4.69 | 6.60 |
| C282 | 42 | — | 0 | 4.80 | 7.85 |
| C230 | 42 | 43 | 1 | 4.00 | 6.20 |
| C280 | 42 | 42 | 2 | 4.80 | 8.05 |
| C231 | 42 | 43 | 3.5 | 6.97 | 6.97 |
| C234 | 42 | 42 | 3.5 | 8.70 | 8.70 |
| C235 | 42 | 42 | 5 | 7.85 | 7.85 |
| C281 | 42 | 42 | 5 | 8.50 | 8.05 |
| C261 | 42 | 42 | 6 | 3.00 | 6.00 |
| C236 | 42 | 42 | 7 | 1.67 | 6.20 |
| C327 | 42 | 42 | 0/7 | 7.90 | 7.90 |
| C288 | 60 | — | 0 | 3.85 | 7.20 |
| C287 | 60 | 43 | 3.5 | 2.58 | 3.09 |
| C289 | 60 | 43 | 5 | 6.85 | 6.85 |
| C303 | 54 | 41 | 6 | 1.75 | 1.65 |
| C307 | 56 | 41 | 7 | 2.20 | 4.62 |
| C290 | 60 | 43 | 7 | 1.95 | 2.50 |
| C312 | 74 | — | 0 | 2.25 | 7.60 |
| C313 | 74 | 56 | 5 | 7.80 | 7.90 |
| C314 | 74 | 56 | 5 | 7.80 | 7.90 |
| C315 | 74 | 56 | 7 | 3.15 | 4.55 |
| C328 | 84 | 43 | 5 | 4.60 | 4.00 |
| C329 | 84 | 43 | 7 | 1.65 | 3.10 |
| C339 | 84 | 42 | 5 | 2.40 | 3.10 |

period of reverse occlusion that followed were quite different, depending on whether the occlusion was applied full-time or part-time, they are described separately below. The kittens were housed with their mothers until weaning in large modified laboratory monkey cages and thereafter in either large custom-built cages (1.2 m long, 0.9 m wide and 0.85 m high) that contained each litter, or else in larger groups in a pen (3 m × 2.4 m) within one of the colony rooms. The colony rooms themselves were illuminated with tungsten lighting on a 16 h light:8 h dark cycle. The conditions of the sutured eyelids were checked carefully every morning for any small openings; in those few kittens in which openings were observed the eyelids were repaired immediately. In addition, the eyes were checked daily for any opacities of the ocular media that could degrade the quality of the retinal image. When such opacities were observed, appropriate treatment was initiated immediately and behavioural testing curtailed. Any animal that did not respond within a few days to treatment was eliminated from the experiment and euthanized.

### (i) *Full-time reverse occlusion*

In this group of animals, reverse occlusion was achieved in the conventional manner by suture of the eyelids of the originally open eye at the same time that the sutured eyelids of the initially deprived eye were parted to restore patterned visual input to that eye. After various periods of reverse occlusion the eyelids of the initially non-deprived eye were opened to allow simultaneous patterned visual input to both eyes for the first time.

### (ii) *Part-time reverse occlusion*

Immediately upon termination of the initial period of monocular deprivation the animals were kept with their mothers in a darkroom for all but 7 h each day. Each day the animals were removed with their mothers from the darkroom for 7 h and placed in an illuminated colony room. Immediately on removal from the darkroom a flexible neoprene foam mask, held in place with velcro fasteners (see Dzioba *et al.* 1986), was placed on their head to occlude the initially non-deprived eye for several hours each day, as indicated in Table 1. For the remaining portion of the period of daily visual exposure the mask was removed to allow simultaneous visual input to both eyes. Immediately after the 7 h of daily visual exposure the animals were

Table 3. *Rearing histories and final visual acuity of 17 monocularly deprived kittens that subsequently received various regimens of occlusion of either one or both eyes*

(NDE, non-deprived eye; DE, deprived eye; B, binocular visual exposure; P, prisms; cont., control prisms, both base-up or base-down; vd, vertical dissociation, one prism base-up, the other base-down; △ prism-dioptre; RO, reverse occlusion, percentages refer to proportion of 7 h day in which occlusion was applied; d, days.)

| | | reverse occlusion regimen | | eventual visual acuity (cycles deg$^{-1}$) | |
|---|---|---|---|---|---|
| cat | monocular deprivation to (days of age) | subsequent daily occlusion regimen | duration (days) | DE | NDE |
| C301 | 42 | NDE (3.5 h); B (3.5 h, $5^{\triangle}$ P cont.) | 42 | 8.15 | 8.15 |
| C300 | 42 | NDE (3.5 h); B (3.5 h, $5^{\triangle}$ P vd) | 42 | 7.75 | 7.75 |
| C333 | 43 | NDE (5 h); B (2 h, $10^{\triangle}$ P cont.) | 41 | 7.30 | 7.25 |
| C299 | 42 | NDE (5 h); B (2 h, $5^{\triangle}$ P vd) | 42 | 8.45 | 8.45 |
| C346 | 42 | NDE (7 h); DE (2 h) | 43 | 0.60 | 0.75 |
| C355 | 42 | NDE (7 h); DE (2 h) | 43 | 1.78 | 1.78 |
| C384 | 42 | NDE (7 h); DE (2 h) | 43 | 3.30 | 1.65 |
| C385 | 42 | NDE (7 h); DE (2 h) | 43 | 3.80 | 1.90 |
| C389 | 42 | NDE (7 h); DE (2 h) | 44 | 2.80 | 2.25 |
| C347 | 42 | NDE (5.5 h); DE (1.5 h) | 43 | 2.78 | 6.40 |
| C419 | 42 | NDE (3.5 h); DE (3.5 h) | 42 | 2.50 | 3.10 |
| C420 | 42 | NDE (3.5 h); DE (3.5 h) | 42 | 2.60 | 3.10 |
| C337 | 42 | NDE (2.33 h); DE (2.33 h); B (2.33 h) | 43 | 5.40 | 2.50 |
| C338 | 42 | NDE (2.33 h); DE (2.33 h); B (2.33 h) | 43 | 2.55 | 3.60 |
| C356 | 42 | NDE (RO, 100%, 42 d → RO, 50%, 25 d) | 68 | 1.52 | 1.90 |
| C357 | 56 | NDE (RO, 100%, 28 d → RO, 50%, 26 d) | 54 | 1.80 | 2.15 |
| C358 | 56 | NDE (RO, 100%, 42 d → RO, 50%, 22 d) | 64 | 3.60 | 3.85 |

returned with their mothers to the darkroom for the next 17 h. After the six- or eight-week period of part-time reverse occlusion the mask was no longer worn, so that both eyes were open simultaneously throughout the period of daily visual exposure; this was maintained at 7 h for about a month or until the visual acuity of the two eyes had stabilized. Thereafter the animals remained in the regular colony rooms. It should be noted that the daily period of visual exposure for those animals that received exclusively binocular visual experience following the initial period of monocular deprivation was also restricted to only 7 h, until the visual acuity of the two eyes had stabilized.

With very few exceptions the animals accepted the masks within 1 or 2 h on the first day, during which time each animal wore a cardboard ruff around its neck to prevent it from removing the mask with its paws. The size of the mask was changed regularly as the animals grew, in order to ensure that the animals were always comfortable. Although the kittens were not monitored directly throughout the 7 h of daily visual exposure (especially on weekends), checks were made as frequently as possible to ensure adherence to the occlusion regimen. Instances of non-compliance, in which the mask had fallen off or had been removed during play, were few; they were usually detected and corrected within 15 min. In such cases the period of occlusion was extended by an amount equal to half the interval that had elapsed between the time when the mask was last observed in place and that when it was found dislodged. Although occasional errors in occlusion time or total exposure duration occurred, the daily period of occlusion was always close to that specified by the particular regimen. To illustrate the degree of compliance with the specified occlusion regimen, the average occlusion times were computed for three representative animals that had been subjected to six weeks of part-time reverse occlusion during which the initially non-deprived eye was occluded for specified times of either 3.5 (C234) or 5 (C235 and C289) h of the 7 h period of daily visual exposure. The mask was never found dislodged from C234 and only fell off once (for no more than 20 min) from C235. The average daily occlusion times for these animals over the six-week period of part-time occlusion were within 0.8% (C235) to 2.8% (C289) of the intended amounts.

The masks were modified for some of the experiments that explored the factors that contributed to the success of certain of the regimens of part-time reverse occlusion. Two animals wore Fresnel prisms before both eyes during the daily (2 h or 3.5 h) period of binocular visual exposure to introduce discordant visual input to the two eyes during this period. Another two control animals also wore prisms during the period of binocular visual exposure, but with identical configurations for the two eyes (base-up or base-down) that produced an equal vertical shift of the images in the two eyes. The prisms (Press-on Optics manufactured by Vision Care/3M, St Paul, Minnesota) were sandwiched between two thin circular pieces of plastic. Small holes were drilled at regular intervals around the circumference to allow the lenses to be stitched to the neoprene foam of the mask (see fig. 2 of Dzioba *et al.* 1986). For three of the animals each prism had a power of five prism dioptres, while for the fourth animal each prism was 10 prism dioptres. The prisms were mounted for two animals with the opposite configuration for the two eyes (base-down for one eye and base-up for the other), which introduced a vertical disparity of 10 prism dioptres between the two retinal images (assuming minimal vertical fusional movements of the eyes). Other rearing regimens examined included several in which each eye was occluded for different parts of the day. To do this, two masks were constructed for each animal that occluded either the initially deprived or non-deprived eye.

### (*b*) *Behavioural testing*

#### (i) *Grating acuity*

Longitudinal measurements of monocular visual acuity were made on a jumping stand (Mitchell *et al.* 1977*b*) by using procedures that have been described in detail in several recent papers (Murphy & Mitchell 1987; Mitchell 1988). The latter papers contain detailed descriptions of all the recent refinements that have been made to the training and testing procedures and that were incorporated into the measurements described in this paper. The following description is therefore very brief and provides only the basic details of the procedure.

The kittens were trained from as early as five weeks old to jump towards a large square-wave grating (19.5 cm × 19.5 cm) that was placed below them and adjacent to a uniform field of the same dimensions and mean luminance (about 100 cd m$^{-2}$). The lateral positions of the two stimuli were interchanged from one trial to the next in a pseudo-random order, with correct jumps rewarded with petting and food (puréed chicken liver) whereas incorrect responses were punished by simple denial of the rewards and immediate repetition of the trial. Daily testing sessions consisted of many blocks of trials with gratings of progressively higher spatial frequencies that were incremented in very small steps (equated on a logarithmic scale) between blocks until a spatial frequency was reached at which the animal could no longer maintain criterion performance. Each testing session began with a grating of very low spatial frequency that was several octaves from the animal's threshold. Typically the animal received only one trial at each of the low spatial frequencies at the beginning of the session unless an error was made, in which case the animal received additional trials at that spatial frequency until it either made five consecutively correct responses or else achieved seven correct responses in a maximum of ten trials. Within an octave of threshold the minimum number of trials at each spatial frequency (assuming flawless performance) was increased to two or three, and for the three or four spatial frequencies closest to threshold the minimum number per block was increased to five. The daily session was terminated at the spatial frequency at which the animal was unable to attain criterion performance as defined above within the maximum number of ten trials allowed at any spatial frequency. Occasionally, where it was suspected that the animal's motivational state was poor, the procedure was repeated once or even twice more, beginning at a spatial frequency one octave below that at which the animal had just failed. As in the past, thresholds on any given day were defined conservatively as the highest spatial frequency for which criterion performance could be maintained. As can be observed in fig. 1 of a previous paper (Murphy & Mitchell 1987), this procedure produces highly repeatable thresholds between sessions in visually mature animals, even in the usual situation where the measurements are made by different experimenters.

Typically, measurements of acuity were made monocularly while the animal wore a large, opaque, contact-lens occluder in the other eye following administration of local anaesthetic (0.5% proparacaine hydrochloride). The only occasions on which thresholds were measured binocularly were during early training and (occasionally) just after the eyelids of an occluded eye were opened, if it was suspected that the eyelids were inflamed. Past work had shown (Giffin & Mitchell 1978) that the binocular acuity was equal to, but did not exceed, the acuity of the better of the two eyes.

Following termination of the initial period of monocular deprivation, or sometimes the period of reverse occlusion that followed, the animal appeared to be blind when forced to use its newly opened eye. The same formal definition for blindness, as assessed on the jumping stand, was employed as in earlier studies (Giffin & Mitchell 1978; Mitchell 1988), namely an inability to locate a closed from an open door on the jumping stand without recourse to tactile information when the jumping platform was placed only a few centimetres above the stimuli. Typically, the animal stepped very cautiously on to the central divider with one paw and used the other paw to search for the closed (safe) door, on which a grating having a large period (40 mm) was placed (see fig. 3.11 of Mitchell (1989)). This operational definition of blindness is designated by the letter 'B' in the figures. However, after a time it became apparent that the animal could locate this door without such a search procedure, as it would step directly on to the door. At this point the platform was raised to force the animal to jump rather than walk on to the grating, to establish in a more formal fashion that the animal had acquired some vision through the particular eye being tested (designated 'O.D.' in the figures). After this ability was achieved the open trapdoor was closed and the negative (uniform) stimulus introduced to test formally for the presence of pattern vision. The ability to make ten consecutively correct jumps to the grating was taken as evidence of pattern vision. After pattern vision had been established, formal longitudinal measurements of visual acuity were begun. In some animals measurements were made of other visual capacities (contrast sensitivity functions and vernier acuity) when the longitudinal measurements of grating acuity indicated that the vision of the two eyes had stabilized.

#### (ii) *Contrast sensitivity functions*

Detailed descriptions of the procedures used to measure contrast sensitivity functions have been described in several earlier papers (Mitchell *et al.* 1984*b*; Murphy & Mitchell 1987; Mitchell 1988). In brief, the two stimuli were generated as a split-screen display on the face of a large oscilloscope display monitor (Joyce Electronics, Cambridge, U.K.). The oscilloscope was mounted with its face pointing upwards so that the stimuli could be viewed by the cat through a sheet of plate glass, which served as the landing surface of the jumping stand and was located 10 cm above the oscilloscope face. A stationary vertical sinusoidal grating, which served as the positive stimulus, was presented on one half of the screen and a uniform field of the same space-average luminance (110 cd $m^{-2}$) on the other half, separated by a thin (1 cm wide) wooden divider on the landing surface. At the usual observation distance of 57 cm, each stimulus was 20° high and 14° wide. Measurements were made of the contrast sensitivity of one eye for gratings of only one spatial frequency on each daily session; the contrast sensitivity of the other eye at the same spatial frequency was measured the next day. Measurements were made first for gratings of the lowest spatial frequency (0.37 or 0.5 cycles $deg^{-1}$) and then for gratings of progressively higher spatial frequency. The order of measurement was then reversed (high spatial frequency to low) and then reversed again until three estimates had been obtained of the contrast sensitivities of both eyes for each spatial frequency. It required about four weeks to generate a complete contrast sensitivity function for both eyes, after which measurements of vernier acuity were begun.

(iii) *Vernier acuity*

Detailed descriptions of the stimulus and training methods for measurements of vernier acuity are provided elsewhere (Murphy & Mitchell 1991). The vernier-grating stimulus was modelled after that devised by Shimojo *et al.* (1984) to measure the vernier acuity of human infants and was similar in some respects to stimuli used by Bradley & Freeman (1985) on adult human subjects. Two computer-generated high-contrast (Michelson contrast = 0.99) square-wave vertical gratings (each grating was 10 cm wide and 14 cm high), separated horizontally by 2.5 cm, were displayed on a display monitor (AMDEK 300, Elk Grove, Illinois). A central region of one of these (carrier) gratings, 3.5 cm high and extending the full width of the grating, was offset horizontally to form multiple vernier offsets (see fig. 1 of Murphy & Mitchell (1991)). This offset region was scrolled smoothly up and down within the central 10 cm of the carrier grating at a velocity of about 0.8° $s^{-1}$. The direction of scrolling was changed in a random fashion and synchronized with a beep from a loudspeaker located below the region between the two carrier gratings. The animals were trained to jump towards the grating with the offset region. Training was begun with a carrier grating of low spatial frequency (about 0.25 cycles $deg^{-1}$) with a vernier offset close to the maximum possible with this type of stimulus, namely half a cycle of the carrier grating.

After the animal had been trained, measurements of vernier acuity were made by first progressively decreasing the magnitude of the vernier offset between blocks of trials in one-pixel (0.3 mm) steps and later, near threshold, by increasing the viewing (jumping) distance in 5 cm steps. The vernier acuity was defined as the smallest displacement that permitted criterion performance, defined (as for all other measurements on the jumping stand) as at least seven correct responses out of a maximum of ten trials at any offset. Vernier acuity was measured for a number of different spatial frequencies of the carrier grating ranging from about 0.25 to 2.7 cycles $deg^{-1}$ for animals with normal grating acuity, but a much smaller range was used for those cats whose grating acuities were impaired. The measurements of vernier acuity at each spatial frequency were repeated until identical acuities were obtained on three consecutive daily test sessions. Because the vernier acuity was determined by changing the size of the vernier offset or by gradually incrementing the observation distance, when the vernier acuities of the two eyes were different the spatial frequencies of the carrier gratings were not always the same for the two eyes.

## RESULTS

### (*a*) *Full-time reverse occlusion*

Previous work (Mitchell *et al.* 1984*b*; Murphy & Mitchell 1987) that examined the long-term consequences of a variety of different periods of initial monocular deprivation and reverse occlusion established that only in one rearing conditions did the vision of both eyes eventually fall within normal values. A similar finding can be obtained from figure 1, which shows results from a second animal (C204) with a very similar rearing history. For comparison, the hatched region indicates the range of values reported for the acuities of normal kittens of different ages by Giffin & Mitchell (1978). During the 35-day period of reverse occlusion the vision of the initially deprived eye recovered from blindness to an acuity of 6.5 cycles $deg^{-1}$. However, upon introducing binocular visual input, the vision of this eye dropped for a few days but then recovered to reach a final level of 5.05 cycles $deg^{-1}$, a value slightly lower than that achieved by the other eye (6.1 cycles $deg^{-1}$). Although these acuities fall just below the range of typical values observed in this laboratory in normal animals (6.4–8.5 cycles $deg^{-1}$), they are substantially better than the eventual values observed in the initially deprived eye of most other monocularly deprived animals that were reverse-occluded at different ages and/or for other durations (see figure 6).

Whereas figure 1 provides an example of the least common observation following termination of reverse occlusion, the more usual situation can be observed in the results of two of the three animals shown in figure 2 whose rearing histories would be thought to improve the chances of the recovery promoted by reverse occlusion being maintained afterwards. One of these situations, namely long periods (12 weeks) of reverse occlusion imposed on monocularly deprived animals quite early in life (at four weeks old), was explored in an earlier paper (Murphy & Mitchell 1987). Figure 2 provides a comparison of results obtained from two animals (C199 and C302) from this earlier study (Murphy & Mitchell 1987) that received this par-

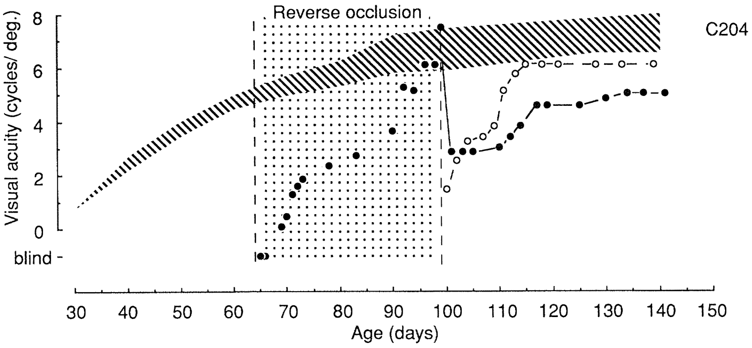

Figure 1. Longitudinal measurements of the visual acuities for square-wave gratings of the initially deprived (filled symbols) and non-deprived (open symbols) eyes of a kitten (C204) that was monocularly deprived from near birth to 64 days old, after which it received a 35-day period of reverse occlusion (indicated by stippling). For comparison, the diagonal hatched region indicates the range of values reported by Giffin & Mitchell (1978) for the acuities of the non-deprived eye of monocularly deprived kittens of different ages. This particular regimen of reverse occlusion resulted in recovery of near-normal visual acuity in both eyes.

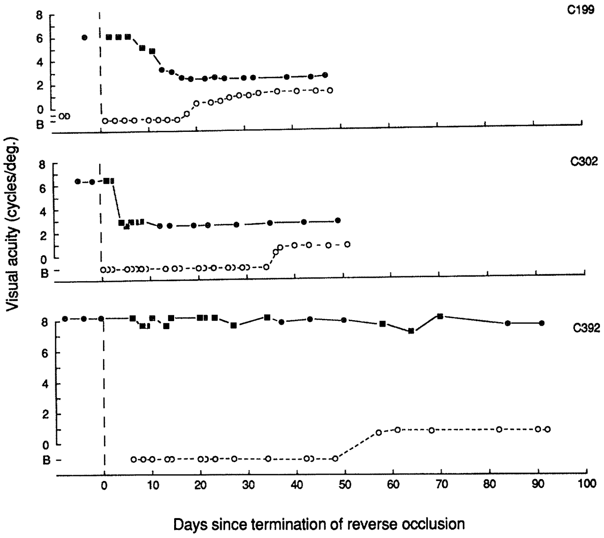

Figure 2. Longitudinal measurements of the visual acuities of the initially deprived (filled symbols) and non-deprived (open symbols) eyes of three monocularly deprived kittens following a 12-week period of reverse occlusion that had been imposed at either 25 (C392) or 28 (C199 and C302) days old. Square symbols are used to depict binocular measurements of acuity and circular symbols refer to monocular measurements made with an opaque contact-lens occluder in the other eye. The letters 'B' and 'OD' on the ordinate refer respectively to the operational definitions of blindness and the ability to discriminate an open from a closed door on the jumping stand. The acuity recovered in the initially deprived eye during reverse occlusion was retained afterwards in only one of these animals (C392).

ticular rearing regimen with findings from another cat (C392) that was reverse-occluded for the same period (12 weeks) but slightly earlier in life, when 25 days old. Despite the fact that the acuity of the initially deprived eye recovered to values of over 6.0 cycles $\text{deg}^{-1}$ by the end of the long period of reverse occlusion, for two of the animals the vision of this eye remained at this high level for only two (C302) to six (C199) days afterwards, subsequently dropping within the next two weeks to values just over 2.0 cycles $\text{deg}^{-1}$. Meanwhile the other eye appeared blind for two to four weeks and thereafter recovered only poor visual acuity of approximately 1.0 cycle $\text{deg}^{-1}$. In contrast to the severe bilateral amblyopia that developed in these two animals, the results obtained from the third animal (C392) were quite different, at least with respect to the eventual outcome for the initially deprived eye. During the 12 weeks of reverse occlusion the visual acuity of this eye recovered to a level (8.2 cycles $\text{deg}^{-1}$) that was at the upper end of the range observed in normal animals. However, in contrast to what occurred in the other animals, the acuity of this eye remained at the same high level following termination of the period of reverse occlusion. Nevertheless, the vision of the initially non-deprived eye showed the same limited recovery as that observed in the equivalent eye of the other animals. Hence the final result was a condition of unilateral rather than bilateral amblyopia (as was observed with C199 and C302) with the initially non-deprived eye as the affected eye.

Although the visual acuity recovered by the initially deprived eye of monocularly deprived animals during a 12-week period of reverse occlusion imposed at about four weeks old was maintained afterwards in only one of three animals, the latter outcome was always observed with even longer periods of reverse occlusion. This particular point is shown in figure 3, which displays the results obtained from three monocularly deprived animals that were reverse-occluded when four weeks old for 16 (C379), 20 (C377) or 24 (C378) weeks. In every case the initially deprived eye retained the high visual acuity it exhibited at the end of the long period of reverse occlusion. Not unexpectedly, the initially non-deprived eye recovered only rudimentary vision (about 1.0 cycle $\text{deg}^{-1}$) following termination of such long periods of reverse occlusion.

Another condition that might be anticipated to result in long-standing, but nevertheless limited, recovery of vision in the initially deprived eye would be if a substantial period of reverse occlusion followed an extended period of monocular deprivation. This particular rearing regimen was explored in one animal (C190) that was reverse-occluded for three months at 20 weeks old. The results from this animal, shown in figure 4, conformed to these expectations. Presumably because of the long initial period of monocular

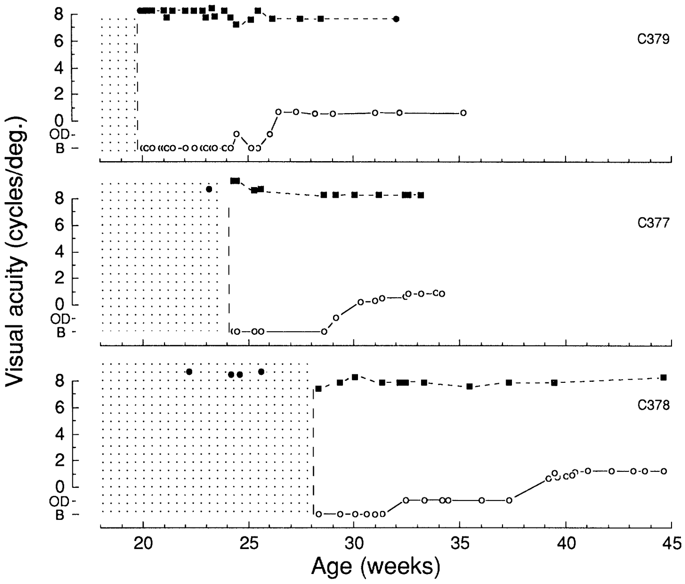

Figure 3. Results of longitudinal measurements made of the visual acuities of the two eyes of three monocularly deprived kittens during the latter stages of a long subsequent period of reverse occlusion (stippled region) and during the period of binocular visual exposure that followed. All three kittens were monocularly deprived until four weeks old and then reverse-occluded for 16 (C379), 20 (C377) or 24 (C378) weeks. Symbols and abbreviations are as for figure 2. The vision recovered during reverse occlusion was retained afterwards.

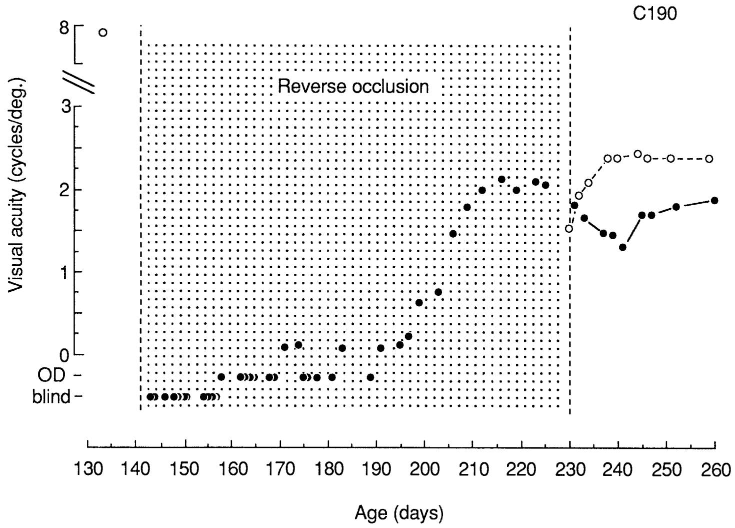

Figure 4. Results of longitudinal measurements of the acuities of the two eyes of a kitten that had been monocularly deprived to 20 weeks old and which had then received an 89-day period of reverse occlusion (stippled region). Symbols and abbreviations as for figure 2.

deprivation, consistent signs of pattern vision were not evident in the initially deprived eye for about seven weeks following reverse occlusion. However, by the end of the three months of reverse occlusion, this eye had attained an acuity of 2.1 cycles $\text{deg}^{-1}$. Although the vision of this eye declined a little subsequently, it soon recovered to a level only slightly below this value. The vision of the initially non-deprived eye was reduced by the long period of reverse occlusion, but recovered a little afterwards to 2.4 cycles $\text{deg}^{-1}$. However, it is important to recognize that despite the rather minor changes in the vision of the two eyes following termination of reverse occlusion, the end result was a situation of severe bilateral amblyopia.

All of the rearing conditions that have so far been described in this and earlier papers have in common the fact that reverse occlusion followed immediately a period of monocular deprivation that had been imposed near birth. To examine the possibility that the rapid changes in the vision of the two eyes that followed reverse occlusion may have had something to do with the purely monocular nature of the prior visual exposure, both the period of monocular deprivation and of reverse occlusion were delayed in two kittens, so as to provide an initial period of binocular vision. Figure 5 displays results from these two animals in which the initial period of monocular deprivation was delayed until the animals were either four (C214) or five (C218) weeks old. Because behavioural training of C214 was not begun sufficiently early, only an approximate estimate of the acuity of the non-deprived eye (indicated by the symbol enclosed by brackets) was

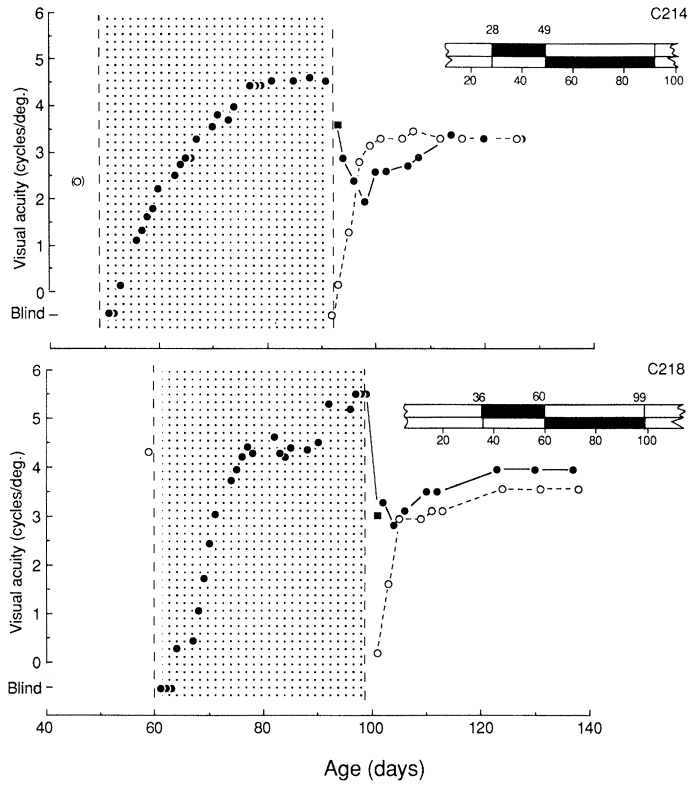

Figure 5. Results of longitudinal measurements of the acuities of both eyes of two monocularly deprived kittens during (stippled region) and following a period of reverse occlusion. Both kittens received normal visual exposure before the period of monocular deprivation, which was initiated at either four (C214) or five (C218) weeks old for 21 and 24 days respectively. The precise rearing histories of the two animals are shown schematically to the right. Symbols are as for figure 2.

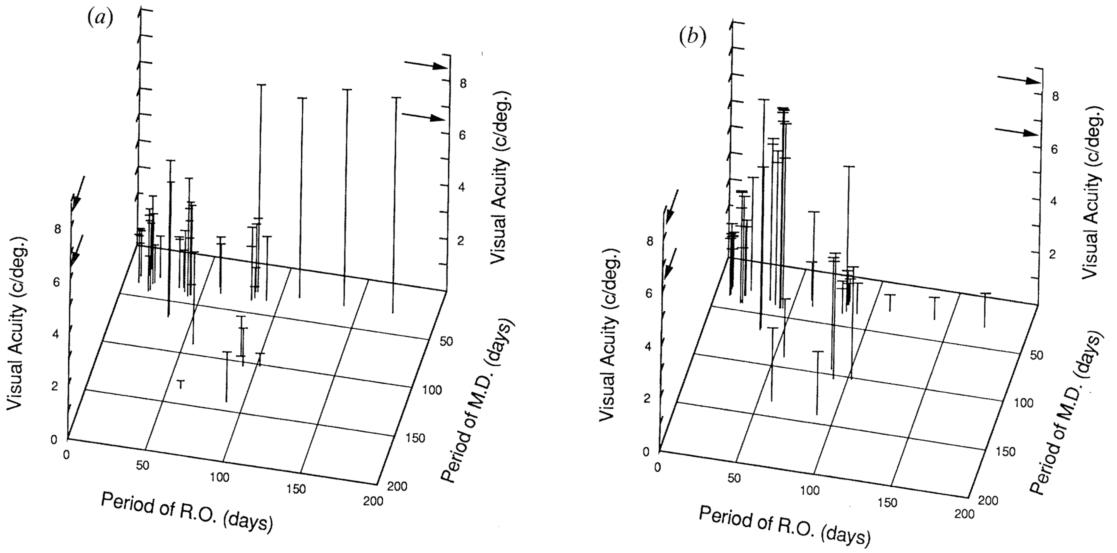

Figure 6. A three-dimensional plot of the final acuities achieved by the initially deprived (*a*) and non-deprived (*b*) eyes of 49 monocularly deprived kittens as a function of the length of the subsequent period of reverse occlusion (R.O.) and the age at which the initial period of monocular deprivation (M.D.) ended and reverse occlusion began. Horizontal ticks depict the results from individual animals. Arrows indicate upper and lower bounds for the monocular acuities of a large population of normally reared animals of comparable ages, tested in our laboratory by the same behavioural procedures.

obtained before the period of reverse occlusion. Just like animals that had been monocularly deprived from near birth, the acuity of the initially deprived eye of both animals dropped rapidly in the days that followed termination of reverse occlusion, while at the same time the vision of the initially non-deprived eye recovered to very similar final values. Although the early period of binocular vision failed to prevent the rapid drop in the acuity of the initially deprived eye in the days following the period of reverse occlusion, the final result was a situation in which the two eyes had vision similar both to each other and to the level that the initially non-

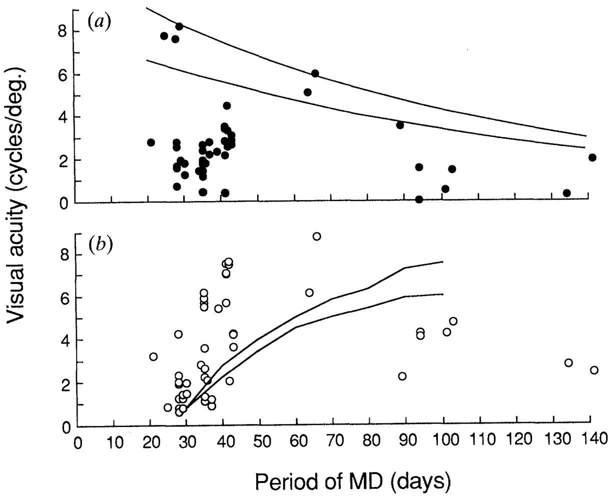

Figure 7. The final acuity of the initially deprived (*a*) and non-deprived (*b*) eyes of the same 49 animals of figure 6 plotted as a function of the length of the initial period of monocular deprivation. The two curves superimposed on the data from the initially deprived eye represent the best fit to data reported previously (Mitchell 1988) on the visual acuity ultimately achieved by the deprived eye of monocularly deprived animals during a subsequent extended period of reverse occlusion (top curve), or in the situation of binocular recovery (bottom curve) where both eyes are open following monocular deprivation. The upper curve permits comparison of the acuity that can be achieved during an extended period of reverse occlusion with that finally observed following a month or more of simultaneous visual input to both eyes after termination of periods of reverse occlusion of various durations. The curves superimposed on the data for the initially non-deprived eyes (*b*) represent upper and lower bounds for the acuities developed at various ages by the non-deprived eyes of four monocularly deprived kittens in an earlier study (Giffin & Mitchell 1978).

deprived eye might have been expected to achieve (C314), or had in fact attained (C218), at the end of the early period of monocular deprivation.

Earlier studies (Mitchell *et al.* 1984*a*, *b*; Murphy & Mitchell 1987) had established that most regimens of reverse occlusion did not result in permanent improvement in the vision of the initially deprived eye of monocularly deprived kittens and that in many circumstances this procedure resulted in long-standing impairment of the vision of the other eye as well. The additional rearing conditions examined in this study have established at least some limits to this phenomenon. In particular, it has been established (see figures 2 and 3) that the deleterious long-term effects of reverse occlusion on the acuity of the initially deprived eye are sometimes circumvented if reverse occlusion is imposed very early in life and maintained for very long periods. Nevertheless, these regimens lead eventually to a severe loss of vision in the other (initially non-deprived) eye. The many other conditions that do not result in long-standing improvement in the vision of the initially deprived eye, or the development of good vision in the other eye, are seen in the three-dimensional graphs of figure 6. These show the final visual acuities of the initially deprived and non-deprived eyes of the 49 monocularly deprived kittens that received various periods of reverse occlusion in this and earlier studies (Mitchell *et al.* 1984*a*, *b*; Murphy & Mitchell 1987). Among the rearing conditions so far explored, the situations in which good vision develops eventually in both eyes are extremely restricted. However, as figure 6 makes clear, there are still a large range of conditions to be explored.

The poor eventual outcome observed as a consequence of the majority of regimens of reverse occlusion so far studied is highlighted in another way in figure 7, which displays the acuity achieved eventually in the initially deprived eye (*a*) and non-deprived eye (*b*) as a function of the length of the initial period of monocular deprivation. The curves superimposed on the data for the deprived eye (*a*) represent the best fit to data reported previously (Mitchell 1988) on the recovery finally achieved in the initially deprived eye either during reverse occlusion (top curve) or in the situation of binocular recovery (bottom curve). Apart from five animals, the vision achieved in the initially deprived eye long after termination of reverse occlusion was always less (usually considerably so) than that which could be attained during extended reverse occlusion or in the passive situation of binocular recovery. The curves superimposed on the data for the initially non-deprived eye (*b*) represent the best fit to data on the development of visual acuity in the non-deprived eye of monocularly deprived kittens (Giffin & Mitchell 1978). These represent the bounds within which the acuity of the initially non-deprived eye would have been expected to lie at the time that the period of reverse occlusion began. It is apparent that in many situations the eventual acuity attained by this eye was little better, or sometimes worse (as happened for periods of monocular deprivation that extended to 90 days old or longer) than the acuity it would have achieved before reverse occlusion. Comparison of the data of figure 7*a* with the curves superimposed on the data of figure 7*b* indicates that in only a very few rearing situations did the vision of the initially deprived eye eventually attain levels that would have been achieved by the other eye before initiation of reverse occlusion.

### (*b*) ***Part-time reverse occlusion***

#### (i) *Monocular deprivation to 6 weeks of age*

Figures 8–10 show the results of longitudinal measurements of the grating acuities of the two eyes of six of the eleven animals from this group that illustrate key features of the findings. The two animals whose results are shown in figure 8 received either no occlusion of the non-deprived eye at all (C282) after the initial period of monocular deprivation, or else received two hours of daily occlusion of this eye (C280) during the six-week period that immediately followed. Because the period of daily occlusion for C280 was so short, the acuity of the initially non-deprived eye during the first ten days of recovery was assessed from measurements of the binocular visual acuity. Although measurements of the acuity of the initially non-deprived eye were measured directly thereafter, the total period of occlusion of the initially deprived eye required for these (ten) measurements over the

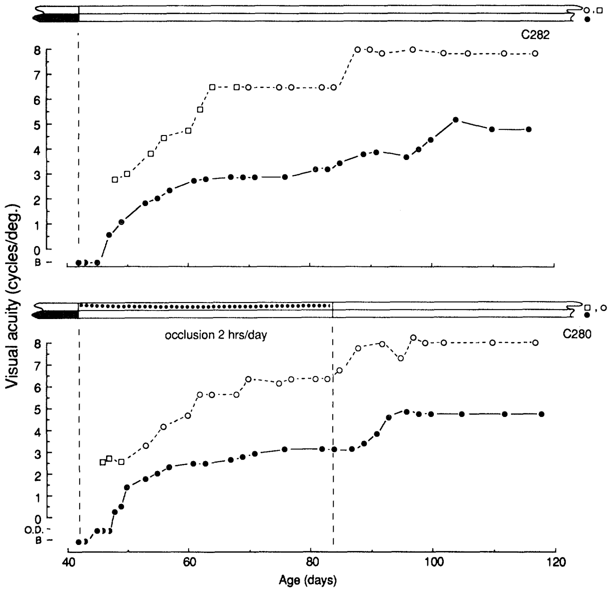

Figure 8. Changes in the visual acuities of both eyes of two monocularly deprived kittens during and following various regimens of occlusion of the initially non-deprived eye imposed for six weeks at six weeks of age. The animal (C282) in the upper part of the figure represents a control condition in which both eyes were open (binocular recovery) following termination of the initial period of monocular deprivation. The other animal (C280) had the initially non-deprived eye occluded by means of a closed-cell neoprene mask for 2 h each day. Both eyes were open for the remaining 5 h of the 7 h of daily visual exposure that each animal received during and following the period over which this regimen of part-time reverse occlusion was imposed. Symbols and abbreviations are as for figure 2. This particular occlusion regimen resulted in recovery of normal visual acuities in both eyes.

following four weeks amounted to less than five hours. The rate and extent of the recovery of vision in the deprived eye of C282, as well as that observed in another animal reared in the same manner (C229), were in accord with findings obtained earlier (Giffin & Mitchell 1978; Mitchell 1988) from animals that had both eyes open throughout recovery from monocular deprivation. However, somewhat surprisingly, the results obtained from the other animal of figure 8, as well as those exhibited by the animal (not shown) that received part-time daily occlusion of the initially deprived eye for only 1 h (C230), were not very different from those obtained from the animals that received no occlusion at all. Neither the rate nor the extent of the recovery of vision of either eye was very different for the two animals of figure 8. This was just as evident during the six-week period that immediately followed the period of monocular deprivation (during which time C280 received part-time reverse occlusion) as it was in the period that followed.

Figure 9 illustrates the remarkable findings observed in the two animals that received 3.5 h of daily occlusion of the initially non-deprived eye (equivalent to 50% of the period of daily visual exposure). During this period of part-time reverse occlusion, the vision of the initially deprived eye improved slightly more than that observed in the equivalent eye of the animals of figure 8. However, unlike the findings observed in the latter animals, the vision of this eye afterwards improved substantially, to approach normal adult values within a month of termination of part-time occlusion. The vision of the initially non-deprived eye also exhibited substantial improvement in the latter period so that eventually both animals achieved normal grating acuities in the two eyes.

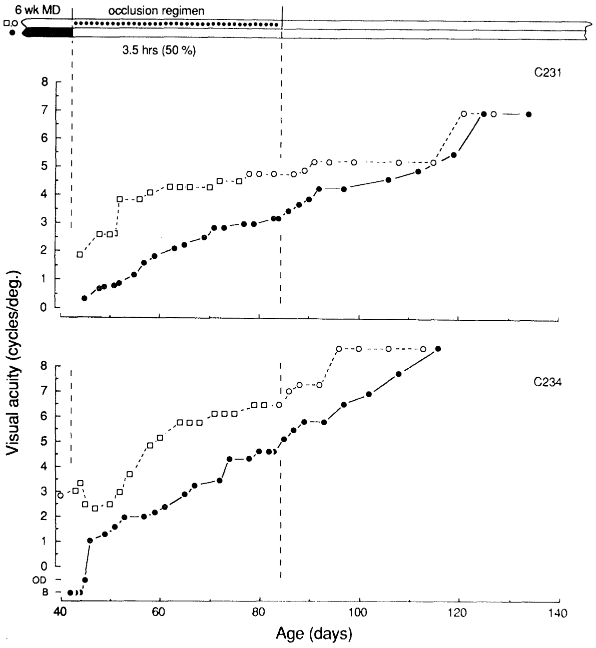

Figure 9. Changes in the visual acuities of both eyes of two monocularly deprived kittens (C231 and C234) during and following the same regimen of occlusion of the initially non-deprived eye imposed for six weeks at six weeks old. The initially non-deprived eye was occluded by a mask for 3.5 h each day, which represented 50% of the period of daily visual exposure. Both eyes were open for the remaining time each day. Symbols and abbreviations are as for figure 2. This particular occlusion regimen resulted in recovery of normal visual acuities in both eyes.

A comparable final outcome was observed in the two animals that received five hours of daily occlusion of the initially non-deprived eye (see figure 1 of Mitchell *et al.* 1986). Unlike the animals that received only 3.5 h of daily occlusion, the vision of the initially non-deprived eye was substantially reduced (see figure 11) during the six-week period of part-time reverse occlusion. However, the vision of this eye rebounded rapidly in the period afterward to approach the visual acuity attained by the other eye in about a month. As might have been anticipated, the vision of the initially deprived eye improved to a greater extent during the six-week period of occlusion than did the equivalent eye of the animals occluded daily for shorter periods of time. The vision of this eye continued to improve following termination of the six-week period of part-time reverse occlusion, to approach normal values in about a month.

The two animals whose results are shown in figure 10 received either 6 h (C261) or 7 h (C236) of daily occlusion. To determine the final effects of these occlusion regimens on the initially non-deprived eye, a single measurement was made of the acuity of this eye

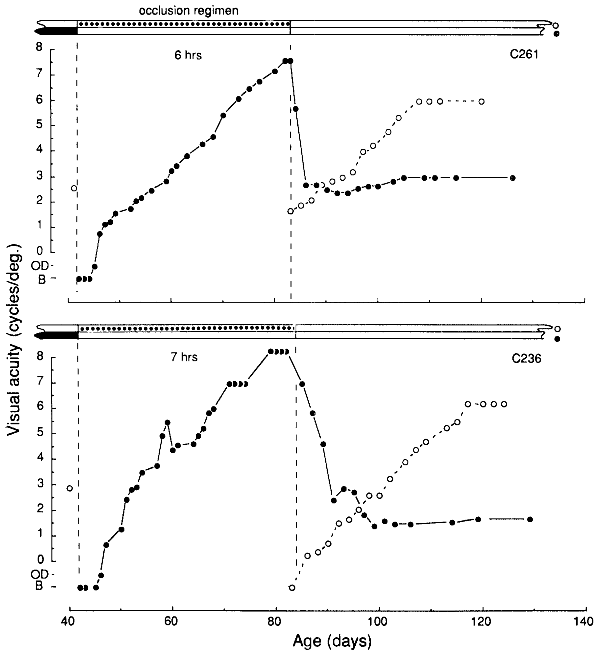

Figure 10. Changes in the visual acuities of both eyes of two monocularly deprived kittens (C261 and C236) during and following two regimens of part-time reverse occlusion that were imposed when the animals were six weeks old for a period of six weeks. Each day the initially non-deprived eye was occluded by a mask for either 6 h (C261) or all 7 h (C236) of visual exposure.

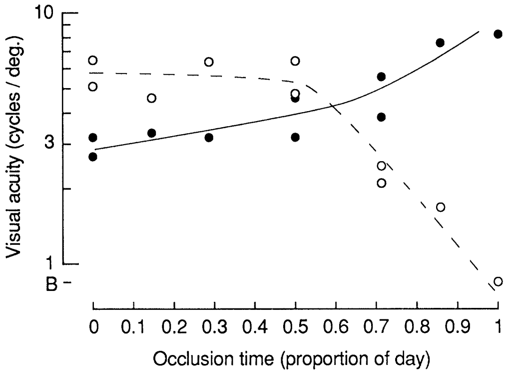

Figure 11. The visual acuity (logarithmic scale) of the initially deprived (filled symbols) and non-deprived eyes (open symbols) of ten monocularly deprived animals immediately before termination of a regimen of part-time reverse occlusion that was imposed after the initial monocular deprivation. All kittens were monocularly deprived to six weeks old, at which time they received one of seven different regimens of part-time reverse occlusion for the next six weeks. The abscissa indicates the proportion of the 7 h day during which the initially non-deprived eye was occluded. The continuous and discontinuous lines have been fitted by eye to the data for the initially deprived and non-deprived eyes, respectively. The letter 'B' on the ordinate indicates that the animal appeared blind on the jumping stand. Occlusion for less than 50% of the daily period of visual exposure had little effect on the acuity of either eye.

during the last day on which these regimens were imposed. The second of these two conditions (occlusion for seven hours) is of course equivalent to full-time occlusion, achieved by means of a mask rather than eyelid suture. However, despite the difference in the method of occlusion, the eventual outcome was very similar to that observed with conventional reverse occlusion by eyelid suture (Mitchell *et al.* 1984*b*). Unlike the outcome observed in the two conditions described above, the substantial visual recovery that occurred in the initially deprived eye during the six weeks of reverse occlusion was not maintained afterwards. Moreover, the vision of the initially non-deprived eye, which was reduced to blindness during the period of reverse occlusion, did not recover to normal levels afterwards. A very similar finding was observed in the animal (C261) that received 6 h of daily occlusion.

The systematic changes that occurred in the vision of the two eyes with increasing daily occlusion time is made even more evident in figure 11, in which the visual acuity achieved by the two eyes at the end of the six-week period of part-time reverse occlusion is plotted as a function of the proportion of time that the initially non-deprived eye was occluded each day. A feature of the findings was the negligible effect of brief occlusion times on the acuity of either eye. Until the occlusion time exceeded 50% of the daily period of visual exposure, the visual acuity of either eye was very little different from that achieved at the equivalent time by the two animals that received exclusively binocular visual experience throughout the recovery period. As occlusion time was increased beyond 50%, the differences between the acuities of the two eyes became progressively larger. Indeed, at the extreme occlusion time (100%), the acuity of the initially deprived eye had recovered to levels within the normal range while at the same time the other eye appeared completely blind.

As the results of figures 8–10 illustrate, the events that occurred upon introduction of simultaneous visual experience to both eyes could not be predicted from the acuities of the two eyes at the end of the period of reverse occlusion (figure 11). The varied eventual effects on the grating acuities of the two eyes were closely mirrored by subsequent measurements of contrast-sensitivity functions and of vernier acuity. Representative findings from measurements of the former conducted on animals from six of the different rearing conditions are shown in figure 12. For the two animals that received exclusively binocular visual exposure during recovery (C229 and C282) there was a 10–20-fold difference between the contrast sensitivities of the two eyes at all spatial frequencies. On the other hand, the contrast-sensitivity differences between the two eyes tended to be greater at low than at high spatial frequencies for the animal (C280) that was occluded for 2 h each day. Like the measures of grating acuity, the contrast-sensitivity functions for the animals occluded daily for 3.5 or 5 h were both within normal limits and equal for the two eyes. Finally, but also in accord with measures of grating acuity, the contrast-sensitivity functions for the animals occluded for 6 h (C261) and 7 h (C236) each day were depressed not only for the initially deprived eye, but also for the other eye as well.

Results of measurements of vernier acuity made on

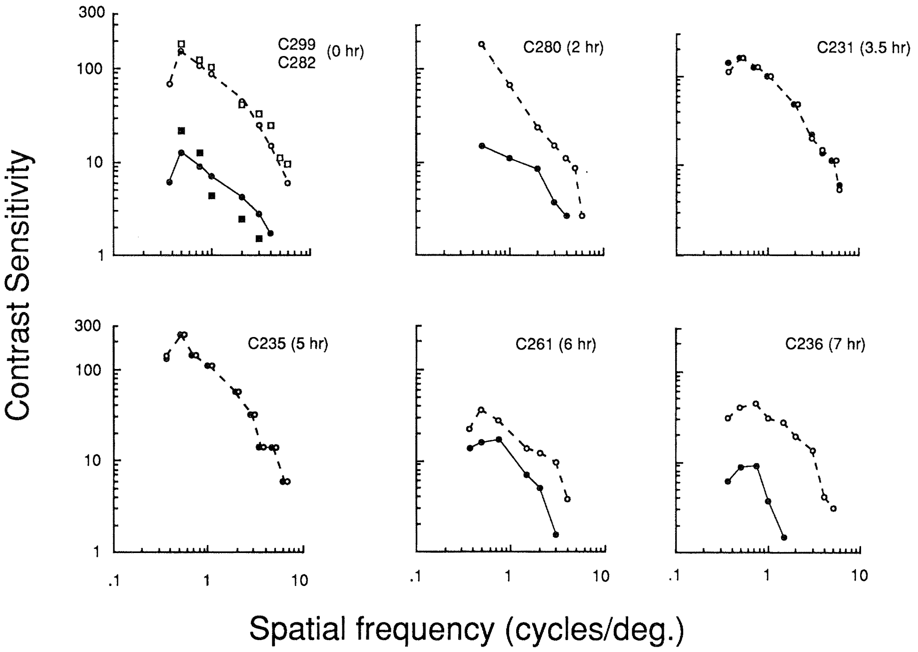

Figure 12. Contrast-sensitivity functions for the initially deprived (filled symbols) and non-deprived eyes (open symbols) of seven monocularly deprived animals that had received various regimens of part-time reverse occlusion as indicated. Each animal was monocularly deprived to six weeks old, and then received various regimens of part-time reverse occlusion for the next six weeks. During the latter period the initially non-deprived eye was occluded by a mask for the time indicated (from 0 to 7 h). The data shown were obtained after the animals had subsequently received at least two months of exclusively binocular visual experience. Data are shown for two animals that received no occlusion of the initially non-deprived eye. The data for C299 are indicated by the circle symbols and the continuous and discontinuous lines, and the square symbols depict data obtained from C282. Contrast was defined as $(I_{\max}-I_{\min})/(I_{\max}+I_{\min})$, where $I_{\max}$ and $I_{\min}$ were the maximum and minimum luminance of the grating display respectively.

four representative animals from the key experimental groups are shown in figure 13. The data are displayed in the way first used by Bradley & Freeman (1985), who used comparable stimuli on human amblyopic subjects. The abscissa of each graph shows the minimum detectable displacement of the offset region within the carrier grating as a function of the spatial frequency of the latter. The dashed oblique line represents the maximum possible offset (equal to half a cycle of the carrier grating) at each spatial frequency. The data for the non-deprived eye of C229, which received binocular visual exposure throughout recovery, were closely comparable to those obtained with identical stimuli from normally reared animals (see figure 2 of Murphy & Mitchell (1991)). As with the latter animals, displacement thresholds for carrier gratings having spatial frequencies below 2.0 cycles $\text{deg}^{-1}$ were very similar (1.2′), but increased substantially at higher spatial frequencies. On the other hand, the displacement thresholds for the deprived eye were substantially worse, by a factor of about 15, than those of the other eye at all spatial frequencies. The best vernier acuity for the deprived eye (18.6′) was in fact lower than the grating acuity of that eye, a finding that has been observed in other monocularly deprived cats, particularly following regimens of reverse occlusion that led to bilateral amblyopia (Murphy & Mitchell 1991).

In striking contrast to the results obtained from C229, the vernier acuities of the animals that received either 3.5 or 5 h of reverse occlusion each day were identical for the two eyes at all spatial frequencies and closely comparable in magnitude to those observed in normal animals. The one minor difference from the latter was the slightly greater reduction in vernier acuity observed at very low spatial frequencies. Finally, the vernier acuities of both eyes of the animal that was reverse-occluded for all 7 h of daily visual exposure were depressed at all spatial frequencies. The best vernier acuity for the initially non-deprived eye (4.1′) was about three times worse than values observed in normal animals, and values for the other eye were virtually identical to those observed in the deprived eye of the animal (C229) that was not reverse-occluded at all. Thus in terms of the effects on both contrast sensitivity and vernier acuity, the eventual outcome was a situation in which the six-week period of effectively full-time reverse occlusion not only conferred no long-term advantage to the initially deprived eye, but also resulted in a permanent impairment of the vision of the other eye.

The eventual effects of the different daily occlusion regimens on three measures of spatial resolution (grating acuity, the reciprocal of the minimum displacement threshold and the peak contrast sensitivity) are shown for comparison for the two eyes of each animal in figure 14. Included in the data on grating acuity are results obtained from the four animals (square symbols), described in the next section, that wore prisms before both eyes during the daily (2 or 3.5 h) period of binocular visual exposure. In two of the animals the prisms had the same orientation for the

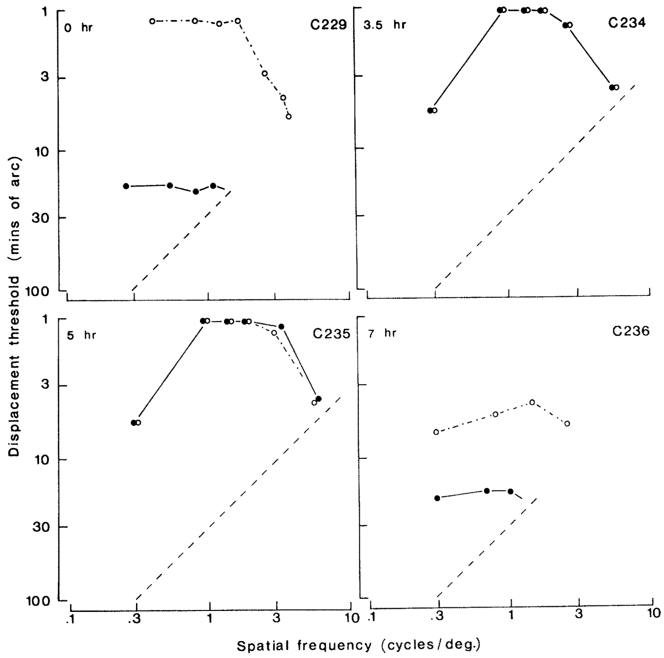

Figure 13. The vernier acuities of the initially deprived (filled symbols) and non-deprived eyes (open symbols) of four monocularly deprived animals that had received one of four different regimens of part-time reverse occlusion as indicated. The ordinate indicates the minimum detectable displacement of the vernier-grating stimulus as a function of the spatial frequency of the carrier grating (abscissa). The dashed line represents the maximum vernier offset (equivalent to half a cycle of the vernier-grating stimulus) that could be displayed at each spatial frequency.

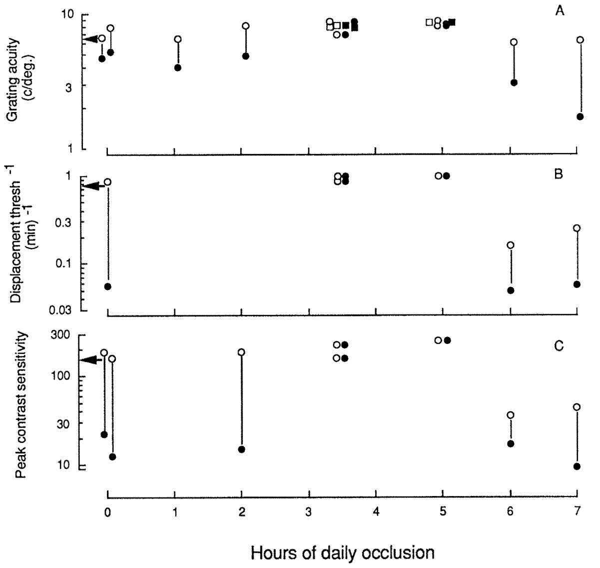

Figure 14. A comparison of the eventual effects of the different daily part-time reverse occlusion regimens on three measures of spatial resolution, namely grating acuity (A), the reciprocal of the minimum displacement threshold (B) and the peak contrast sensitivity (C). Filled and open symbols depict data for the initially deprived and non-deprived eyes respectively. Vertical lines join data from the two eyes of individual animals. The arrows to the left provide a lower bound for values for the three measures observed in normal animals under similar test conditions. Animals that were occluded daily for either 3.5 or 5 h achieved normal levels of performance on all three measures.

two eyes, and so caused an equal vertical shift of the two retinal images. However, in the other two animals the prisms were mounted with the opposite configurations for the two eyes, to introduce a vertical misalignment and hence a discordance between the two retinal images. Interestingly, the extent of the eventual visual recovery in these different situations was identical; like the animals described above that were subjected to the same occlusion regimen, both eyes recovered normal grating acuities. The data of figure 14 illustrate both the beneficial effects for both eyes of the 3.5 and 5 h occlusion times on all three visual measures and the unsatisfactory outcomes associated with all the other rearing conditions. In terms of the various unsuccessful occlusion times, it is of interest to note that on two of the three visual measures (vernier acuity and peak contrast sensitivity), the vision of the initially deprived eye was reduced from normal values by a similar amount. Moreover, the data of figure 14 also emphasize the close similarity of the effects on the three visual measures of the two longer occlusion times. In particular, the results emphasize the detrimental effects of these particular occlusion times on the vision of the initially non-deprived eye.

A simple variant of one of the successful occlusion times (the 50% condition) was examined in one kitten (C327). Instead of halving each daily period of visual exposure into 3.5 h intervals of monocular followed by binocular visual exposure, the alternating visual experience was extended over two days so that on one day the initially non-deprived eye was occluded for all 7 h, whereas on the next day both eyes were open throughout the period of visual exposure. As indicated schematically at the top of figure 15, which displays the results obtained from this animal, the six-week period over which this regimen of occlusion was imposed began and ended with binocular visual exposure. As with the animals (figure 9) that received equivalent occlusion but on a daily basis, the grating acuities of the two eyes continued to improve on values achieved at the end of the period that the occlusion regimen was imposed, to reach levels within the normal range in about a month. The extent of visual recovery in the two eyes was subsequently confirmed by measurements of contrast-sensitivity functions for the two eyes (see figure 15 inset), which were indistinguishable from those observed in normal animals.

### (ii) *Monocular deprivation to eight weeks old*

Longitudinal measurements of visual recovery were made during and following imposition of six weeks of part-time reverse occlusion on six kittens that were monocularly deprived to about eight weeks old (range 54–60 days). Results of such measurements made from four of these animals (all litter-mates) are shown in figure 16. One of these animals (C288) received no occlusion of the initially non-deprived eye, whereas the others had this eye occluded daily for 3.5 h (C287), 5 h (C289) or all 7 h (C290) of daily visual exposure. Whereas daily occlusion times of 3.5 and 5 h both led to the eventual recovery of good vision in both eyes of

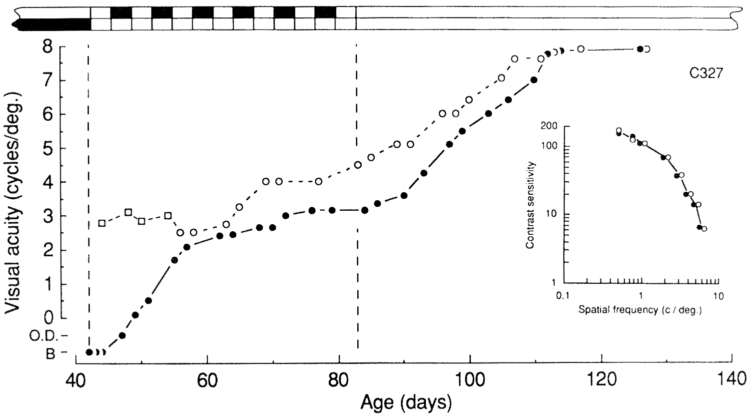

Figure 15. Longitudinal measurements of the visual acuity of the initially deprived and non-deprived eyes of a monocularly deprived kitten (C327) that subsequently received a variant of the 50% part-time reverse occlusion regimen, in which the initially non-deprived eye was occluded for all 7 h of daily visual exposure on alternate days but not occluded at all on the intervening days. The inset displays the contrast-sensitivity function for the two eyes of this animal measured after completion of the longitudinal measurements of visual acuity.

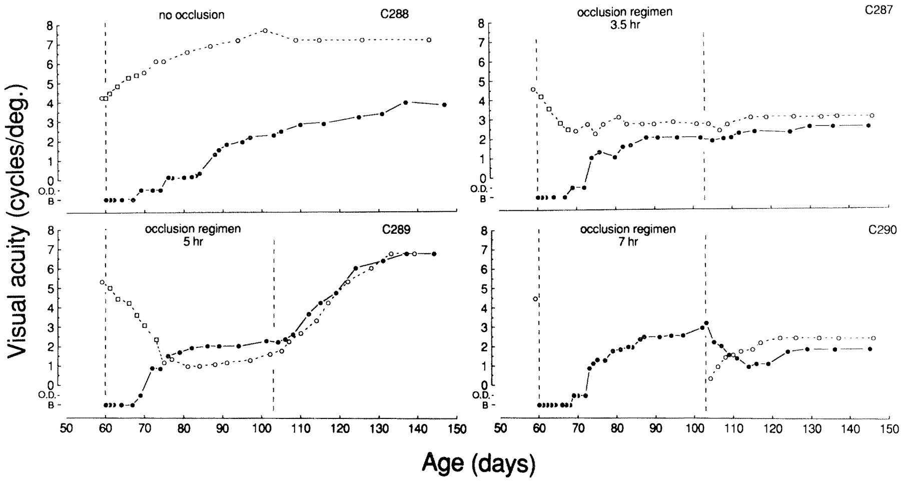

Figure 16. Longitudinal measurements of the visual acuities of the initially deprived and non-deprived eyes of four monocularly deprived kittens during and following subsequent imposition of the four different regimens of part-time reverse occlusion indicated. All four animals were monocularly deprived to 60 days old, at which time they received one of four regimens of part-time reverse occlusion for six weeks. Symbols and abbreviations are as for figure 2.

animals that were monocularly deprived to six weeks, the limited data suggest that only the latter exposure condition produced the same outcome in animals deprived to eight weeks. In contrast to the substantial improvement that occurred in the vision of both eyes of C289 after cessation of the occlusion regimen, very little change occurred in the vision of either eye of C287 in this same period, with the result that this animal developed bilateral amblyopia. A similar final outcome was observed in the fourth animal (C290), which received 7 h occlusion of the initially non-deprived eye each day. As observed frequently with full-time reverse occlusion by eyelid suture, the vision of the initially deprived eye declined rapidly after visual experience was exclusively binocular, while the vision of the other eye improved to only modest levels, in this case to levels that were substantially less than the acuity that had been achieved by this eye during the initial period of monocular deprivation. A very similar pattern was observed in the animal (not shown) that received six hours of daily occlusion. The substantial visual recovery exhibited by both eyes of the animal on which the five-hour occlusion regimen had been imposed was evident not just in terms of grating acuity but was also reflected in measures of vernier acuity and contrast sensitivity. Limited data obtained from this animal on the former as well as contrast-sensitivity functions for both eyes are shown in figure 17. Thresholds were identical for both eyes and within the range of values observed in normal animals.

The overall pattern of visual acuities reached by each eye of this group of animals at two points in time are summarized in figures 18 and 19. Figure 18 shows, as a function of the daily occlusion time, the acuities that were attained at the end of the period of part-time reverse occlusion; figure 19 displays the acuities that were achieved subsequently by the two eyes when visual experience was exclusively binocular. Because no measurements were made of the acuity of the initially non-deprived eye of the three animals that received either 6 or 7 h of daily occlusion of this eye during the six-week period of part-time reverse occlusion, the acuity of this eye indicated in figure 18 was that measured a day after introduction of

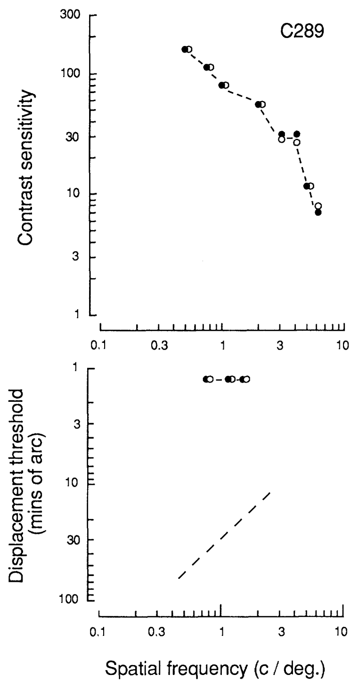

Figure 17. Contrast-sensitivity functions and vernier acuities of the initially deprived (filled symbols) and non-deprived eyes (open symbols) of C289, an animal that had been monocularly deprived to 60 days old and which had then for the next six weeks received a regimen of part-time reverse occlusion, in which the initially non-deprived eye had been occluded for 5 h each day. As shown in figure 16, this animal eventually recovered normal visual acuities in the two eyes. The dashed line in the lower graph indicates the largest vernier offset that can be produced by the vernier-grating stimulus at each spatial frequency.

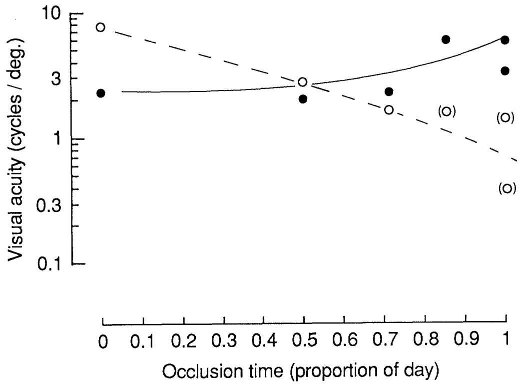

Figure 18. The visual acuities (logarithmic scale) of the initially deprived (filled symbols) and non-deprived (open symbols) eyes of six animals that had been monocularly deprived to between 54 and 60 days old immediately before termination of various regimens of part-time reverse occlusion that were imposed immediately afterward for six weeks. The abscissa indicates the proportion of the 7 h of total daily visual exposure that the initially non-deprived eye was occluded in this latter period. The continuous and discontinuous lines have been fitted by eye to the data for the initially deprived and non-deprived eyes respectively.

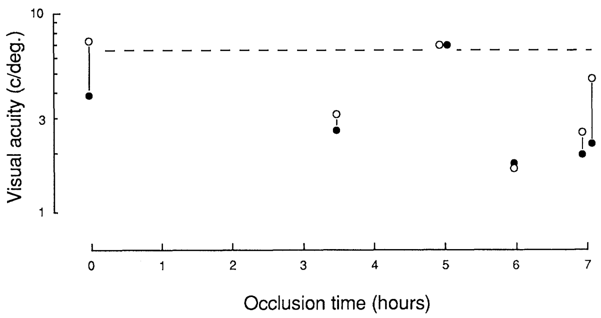

Figure 19. The final visual acuities of the initially deprived (filled symbols) and non-deprived (open symbols) eyes of the same animals as shown in figure 18, after at least a month of binocular visual exposure. The abscissa indicates the daily period of occlusion of the initially non-deprived eye during the period of part-time reverse occlusion. Vertical lines join data from the two eyes of individual animals.

simultaneous visual input to the two eyes. Consequently it is possible that these measurements (indicated by symbols surrounded by brackets) may overestimate the actual acuity of this eye at the end of the period of part-time reverse occlusion. Although the data are more limited, the findings are similar to those shown in figure 11 from the animals that had been monocularly deprived to six weeks old. As with the latter group of animals, occlusion of the non-deprived eye for 50 % or less of the daily period of visual exposure resulted in little change in the acuity of the initially deprived eye. However, the limited data suggest that such short occlusion times did reduce the acuity of the other eye. Longer occlusion times resulted in increasing improvement in the vision of the initially deprived eye accompanied by substantial erosion of the vision of the other eye. However, as with the animals described earlier (figure 14), the acuities seen at the end of the period of part-time reverse occlusion were very different from those observed a month or so later after introduction of exclusively binocular visual input (figure 19). In only one condition (daily occlusion for 5 h) did the acuity of both eyes attain values within normal limits, and in only one other condition did the vision of even one eye (the initially non-deprived eye of the animal that received no occlusion) attain this eventual level. All the other animals developed bilateral amblyopia.

### (iii) *Monocular deprivation to 10 and 12 weeks old*

The effectiveness of several different regimens of part-time reverse occlusion were examined in a limited number of animals that had been monocularly deprived until either 74 ($n = 4$, all litter-mates) or 84 ($n = 3$) days old. Because of the poor eventual outcome observed when daily periods of reverse occlusion of less than 5 h were used on animals that had been monocularly deprived to eight weeks old, only the consequences of daily reverse occlusion times 5 h or more were examined in animals deprived initially for longer periods. In addition, the duration of the period of part-time reverse occlusion was extended from six to eight weeks for the animals that had been monocularly deprived to 10 weeks old.

The results of longitudinal measurements of the grating acuities of the two eyes of three kittens from the 10 week group that received either no reverse occlusion (C312) or else 5 h or 7 h of daily occlusion are given in

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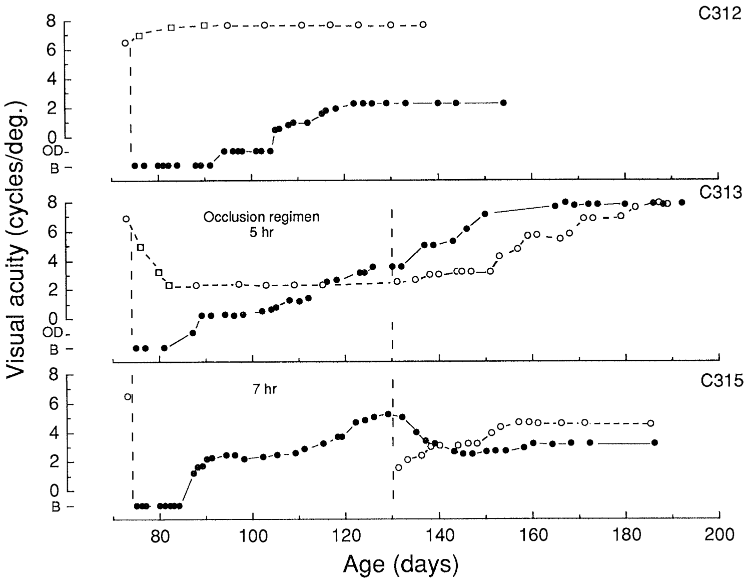

Figure 20. Longitudinal measurements of the visual acuities of the initially deprived and non-deprived eyes of three kittens that had been monocularly deprived to 74 days old during and following the subsequent imposition of an eight-week period of part-time reverse occlusion. The animal at the top of the figure (C312) did not receive any occlusion of the initially non-deprived eye after the initial period of monocular deprivation, whereas the other two received the two regimens indicated. Symbols and abbreviations are as for figure 2.

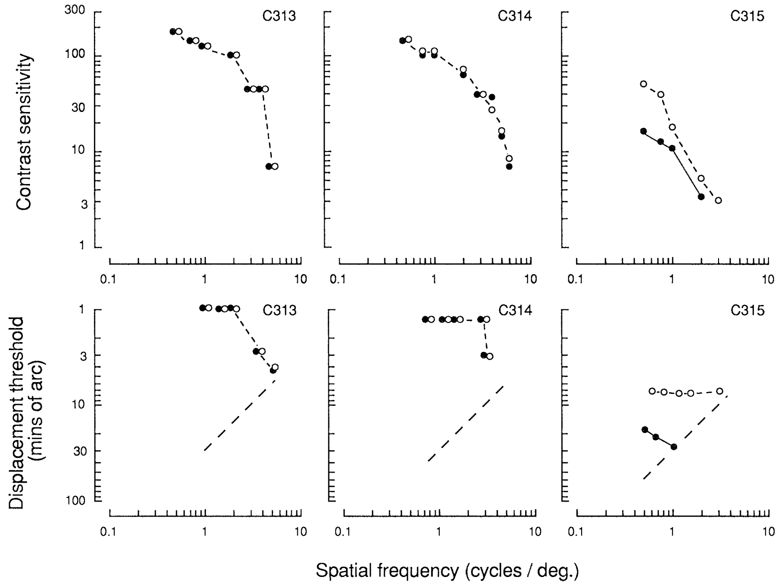

Figure 21. Contrast-sensitivity functions (top) and vernier acuities (bottom) of the initially deprived (filled symbols) and non-deprived (open symbols) eyes of three animals that had been monocularly deprived to 74 days of age and which had for the next eight weeks received either of two regimens of part-time reverse occlusion. For two of the animals, C313 and C314, the initially non-deprived eye was occluded for 5 h each day during the latter period whereas the third animal (C315) had this eye occluded for all 7 h of daily visual exposure. The dashed line in the lower graphs represents the largest vernier displacement that could be produced with the vernier-grating stimulus at each spatial frequency.

figure 20. As with the two groups of animals that were initially deprived for shorter periods of time, during the period of part-time reverse occlusion there was a systematic increase in the acuity attained by the initially deprived eye with increasing amounts of daily occlusion that was accompanied by a progressive reduction in the acuity of the initially non-deprived eye. However, as with the other groups, following a month of exclusively binocular visual input the acuities of the two eyes were no longer related to the length of the prior daily occlusion time in such a simple monotonic fashion. The animal that received no reverse occlusion (C312) eventually recovered an acuity of only 2.25 cycles deg$^{-1}$ with its deprived eye but normal acuity (7.60 cycles deg$^{-1}$) with the other eye. At the other extreme, the animal (C315) that received 7 h of daily reverse occlusion recovered only slightly better acuity with its initially deprived eye (3.15 cycles deg$^{-1}$), but the eventual acuity attained by the other eye was both substantially below normal levels and lower than the value it had achieved much earlier (6.4 cycles deg$^{-1}$) before the start of the period of daily

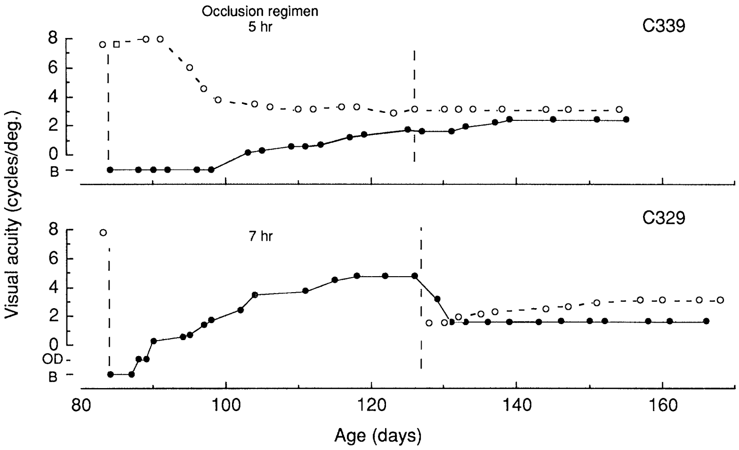

Figure 22. Longitudinal measurements of the visual acuities of the initially deprived and non-deprived eyes of two animals that had been monocularly deprived to 12 weeks old and which had then received the indicated regimens of part-time reverse occlusion for the next six weeks. Symbols and abbreviations are as for figure 2.

occlusion. However, as with the animals deprived to eight weeks old, only C313 and C314 (table 2) that received an intermediate amount (5 h) of daily occlusion of the initially non-deprived eye recovered normal visual acuities in both eyes. A very similar picture emerged from measurements made subsequently of contrast-sensitivity functions and vernier acuity. Results of these measurements from the two animals that recovered normal visual acuities in both eyes (C313 and C314) as well as the cat that received 7 h of daily occlusion (C315) are displayed in figure 21. The contrast sensitivities as well as vernier acuities of the two eyes of C313 and C314 were equal at all spatial frequencies that were examined, and moreover the peak contrast sensitivities and best vernier acuities were similar to those observed among normal animals. In contrast, the vernier acuities and contrast sensitivities of the two eyes of C315 were well below normal at all spatial frequencies.

Only a few animals monocularly deprived to 12 weeks old have been studied to date. Subsequently, each of these received only a six-week period of reverse occlusion, similar to that experienced by the animals that were deprived to six or eight weeks old. Results of longitudinal measurements of grating acuity made on two of the three animals from this group, but representative of the only two occlusion regimens examined (5 h and 7 h of daily occlusion), are displayed in figure 22. Both these animals, as well as the third animal (not shown) that also received 5 h daily part-time reverse occlusion (C328), ultimately developed bilateral amblyopia in response to these occlusion regimens. The severity of this bilateral amblyopia was revealed in a more graphic fashion from measurements of contrast sensitivity and vernier acuity. For example, the peak contrast sensitivity (at 0.75 cycles $\deg^{-1}$) for C339 was 15.6 for the initially non-deprived eye, an order of magnitude below normal values, and considerably less (2.6) for the other eye. The peak contrast sensitivities for C329, the animal that received 7 h of daily occlusion, were only 8.8 and 4.9 for the initially non-deprived and deprived eyes respectively. The vernier acuity of this animal, the only animal from this group from which such measurements were made, was severely reduced to between 24′ and 28′ for both eyes, values that were nearly a factor of 20 above normal levels.

### (*c*) *Factors that contribute to the success of some regimens of part-time reverse occlusion*

#### (i) *Concordant as opposed to discordant binocular visual exposure*

The most obvious difference between part-time and conventional full-time reverse occlusion is the fact that the former incorporates a daily period of binocular visual exposure. However, the experiments so far described do not identify the conditions pertaining to the latter period that were necessary in order for a beneficial outcome. Most importantly, they do not distinguish between three possible requirements. The most stringent possibility is that it is necessary for the two eyes to receive simultaneous and concordant visual input each day. Alternatively, it may be necessary only for the two eyes to receive daily simultaneous visual exposure. Finally, it may be sufficient only for the two eyes to receive visual input each day, but not necessarily simultaneously. To distinguish between the first two of these possible requirements an optical misalignment between the two eyes was introduced deliberately, by means of prisms, during the daily period when both eyes were open, to introduce discordant visual input to the two eyes. This was achieved by having the animals wear a mask that contained Fresnel prisms in front of both eyes; the prisms had opposite configurations for the two eyes during the daily period of simultaneous binocular visual exposure (see § 2, Methods).

This study was done on four kittens (three of which were litter-mates) that had been monocularly deprived to six weeks old, after which they received either of the two regimens (3.5 or 5 h of daily occlusion of the initially non-deprived eye) of part-time reverse occlusion that the earlier experiments had shown lead to the development of normal grating acuities in the two eyes. Two kittens (C299 and C300) were assigned to each of the two occlusion regimens; one of each pair wore prisms that introduced a vertical disparity between the two images, and the other served as a control in which both prisms had the same orientation.

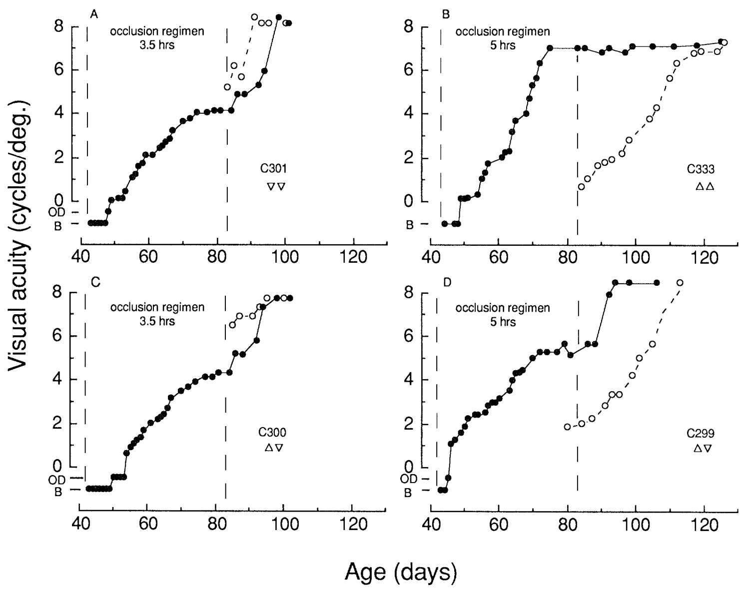

Figure 23. Longitudinal measurements of the visual acuities of the initially deprived and non-deprived eyes of four monocularly deprived kittens during and following two regimens of part-time reverse occlusion (3.5 and 5 h of daily occlusion of the initially non-deprived eye) imposed for six weeks at six weeks old. During the daily period of binocular visual exposure, and throughout the period of exclusively binocular visual exposure that followed, each kitten wore a mask that contained prisms in front of each eye. For two kittens, C301 and C333, the prisms had the same orientation for the two eyes, whereas for the other two animals the prisms had opposite configurations for the two eyes (base-down for one eye and base-up for the other) to introduce a vertical disparity between the two retinal images. Symbols and abbreviations are as for figure 2. All four animals achieved normal visual acuities in both eyes.

The prisms were worn not only during the six-week period of part-time reverse occlusion, but also for a period of at least a month afterwards, until the acuities of the two eyes had stabilized. In this latter period the prisms were worn for all 7 h of visual exposure. For three kittens each prism was five prism-dioptres so that in the situation where they were of opposite configuration a vertical disparity of 10 prism-dioptres (about 5°) was introduced between the two eyes. Prisms of higher power (10 prism-dioptres) were used for the fourth kitten (C333), which was assigned to the control condition in which the two prisms had the same configuration (base-down) for the two eyes, thereby introducing no disparity between the two retinal images.

The results of longitudinal measurement of the acuities of the two eyes of all four kittens during and following the period of part-time reverse occlusion are shown in figure 23. No measurements of the acuity of the initially non-deprived eye were made during the period of part-time reverse occlusion on three of the kittens, but a single measurement was made of the acuity of this eye of C299 just before the end of this period. The data for both animals that received 3.5 h daily part-time reverse occlusion, both during and after this period, were quite similar to that observed in the two animals described earlier (figure 9) that did not wear prisms. Significantly, like these animals, both C300 and C301 developed normal visual acuities in both eyes. Although the recovery observed in the initially deprived eye of C333 was slightly greater than that observed with C299 or among the animals described earlier that did not wear prisms and on which a similar occlusion regimen had been imposed, the final outcome was identical. The fact that all four animals attained normal visual acuities in both eyes, irrespective of the relative configuration of the prisms worn during the daily period of binocular visual exposure, implies that visual input during this period need only be simultaneous but not concordant for the vision of the two eyes to recover to such levels. This raises the possibility that it may only be necessary for the two eyes to receive visual input each day, but not necessarily simultaneously, a possibility that was explored in a series of animals for which both eyes received visual experience each day, but successively rather than at the same time.

### (ii) *Simultaneous as opposed to successive daily visual experience for the two eyes*

As described above, the 5 h part-time occlusion regimen comprised a 5 h daily period of occlusion of the initially non-deprived eye followed by 2 h of binocular visual exposure. However, in terms of the daily amount of visual exposure received by each eye, this regimen is equivalent to a period of exposure of the initially deprived eye that extends throughout the 7 h of daily visual exposure, together with a 2 h period of exposure of the initially non-deprived eye, the latter obtained during the time when both eyes were open. On the basis of the previous experiment (figure 23), it would appear that the visual input during the latter period need not be concordant for the visual acuity of the two eyes to recover to normal levels, thereby raising the further question as to whether the success of this regimen depends upon a daily period of simultaneous (but not concordant) visual exposure of the two eyes or whether it instead requires only that each eye receives

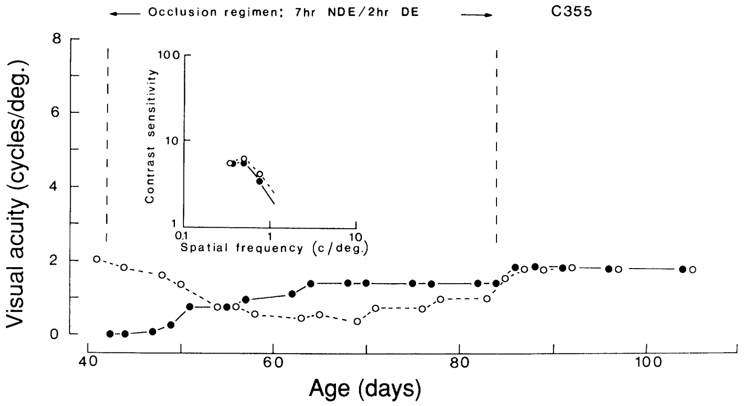

Figure 24. Longitudinal measurements of the visual acuities of the initially deprived (filled symbols) and non-deprived (open symbols) eyes of a kitten (C355) that had been monocularly deprived to six weeks old, and that had for the next six weeks received a regimen of daily alternating occlusion of the two eyes in which first the initially non-deprived eye was occluded for 7 h and then the initially deprived eye was occluded for 2 h. Contrast-sensitivity functions for the two eyes measured two months after completion of the longitudinal measurements of visual acuity (see inset) reveal the severity of the bilateral amblyopia that resulted from this particular occlusion regimen.

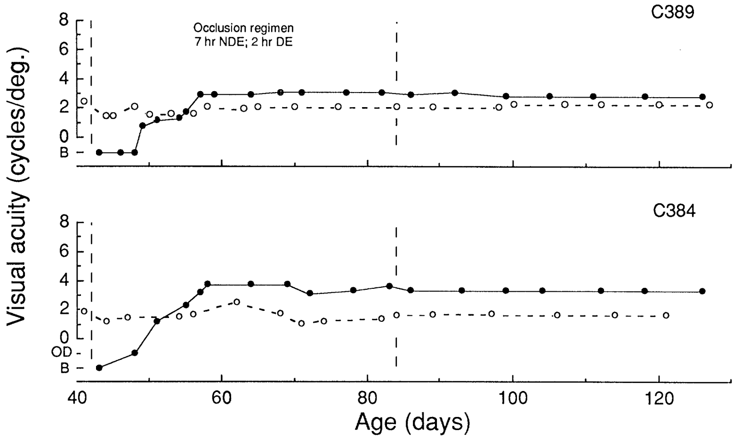

Figure 25. Longitudinal measurements of the visual acuities of two more monocularly deprived animals that subsequently received the same occlusion regimen as the animal of figure 24 and that also developed severe bilateral amblyopia. Symbols and abbreviations are as for figure 2.

visual input, but not necessarily at the same time as the other. The latter possibility was examined on a total of eight kittens that had been monocularly deprived to six weeks old. Five of the animals (see table 3) received subsequently for six weeks a daily period of alternating monocular exposure, in which, first, the initially deprived eye received visual experience for 7 h, followed by a 2 h period of exclusive exposure of the initially non-deprived eye. In terms of the total daily visual experience received by each eye, this regimen was identical to the successful 5 h (or 70 %) part-time reverse occlusion regimen examined above. A sixth animal (C347) received the approximate equivalent proportional exposure of the two eyes associated with the same successful part-time reverse occlusion regimen, but divided between the two eyes so that the total visual exposure was 7 rather than 9 h. In this case the initially deprived eye was exposed for 5.5 h, which was very close to the equivalent proportional exposure ($\frac{7}{9}$ of 7 h, or 5.45 h), while the other eye was exposed for 1.5 h. The remaining two animals (C419 and C420) each received an equal period of alternating exposure of the two eyes of 3.5 h, beginning with the initially deprived eye. Many of the (larger number) of animals assigned to the first set of exposure conditions were reared primarily for the purposes of a concurrent anatomical study.

The final visual acuities (see table 3) for all but one of the eight animals were very different from those described earlier from the animals that received a daily period of binocular visual exposure. All but one of the animals developed bilateral amblyopia, which in two of the animals (C346 and C355) was extremely severe. The one animal (C347) that would not be defined as having bilateral amblyopia on the basis of the visual acuity of its initially non-deprived eye (6.4 cycles $\text{deg}^{-1}$) nevertheless would be so classified on the basis of the contrast-sensitivity function of this eye, which was quite depressed. Figure 24 shows the results of longitudinal measurements of the acuities of the two eyes of C355, one of the two animals that developed the most severe bilateral amblyopia, made both during and after the occlusion regimen. The contrast-sensitivity functions for the two eyes, measured after completion of the longitudinal measurements, are displayed as an insert. The contrast sensitivity of both

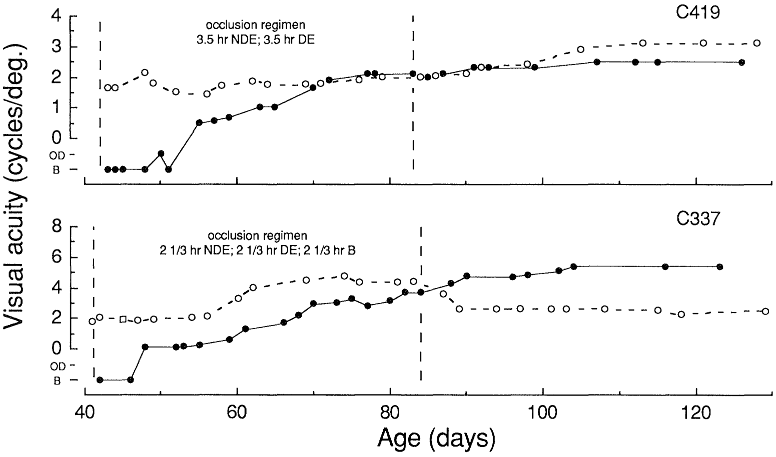

Figure 26. Longitudinal measurements of the visual acuities of the initially deprived and non-deprived eyes of two kittens that had been monocularly deprived to six weeks old and which for the next six weeks received one of the two different occlusion regimens indicated. During the latter period for C419, first the initially non-deprived eye was occluded for 3.5 h, and then the other eye was occluded for the same time. For C337 the occlusion regimen was more complex, beginning with occlusion of the initially non-deprived eye, followed by occlusion of the other eye and concluding with a period of binocular visual exposure, all for the same duration, namely 2.33 h. Symbols and abbreviations are as for figure 2. Both animals developed bilateral amblyopia.

eyes was extremely poor at all spatial frequencies. Even at its best, at 0.5 cycles $\text{deg}^{-1}$, contrast sensitivity was a factor of 25 below normal values. The severity of the bilateral amblyopia that developed in C346 was the most profound encountered as a consequence of any of the occlusion regimens explored so far. The final acuity of the better of the two eyes was only 0.75 cycles $\text{deg}^{-1}$ (table 3). Attempts were made to measure the contrast sensitivity of this eye at 0.5 cycles $\text{deg}^{-1}$, but the animal was unable to learn the task even with gratings having a contrast of 0.5. Intermittent pendular nystagmus was noted in both eyes of this animal at nine months old.

The results of longitudinal measurement of acuity made on both eyes of two other animals representative of the others from this group (C384 and C389) that developed less severe bilateral amblyopia are given in figure 25. Interestingly, the initially deprived eye of C384 eventually attained a higher acuity (3.30 cycles $\text{deg}^{-1}$) than did the other eye (1.65 cycles $\text{deg}^{-1}$). Finally, the results obtained from the two animals on which the other regimen of alternating occlusion (3.5 h for each eye) had been imposed after the initial period of monocular deprivation (C419 and C420) were very similar in that the final result was again a situation of bilateral amblyopia. Figure 26 shows the results of longitudinal measurements of the acuity of the two eyes of one of these animals (C419); the severity of the bilateral amblyopia that developed in this animal as well as its litter-mate (C420) that was subjected to the same occlusion regimen was very similar to that observed in the eight animals described above. A similar final outcome was observed in two other kittens (C337 and C338), for which each day successive exposure of each of the two eyes in turn (for 2.33 h) was followed by a period of binocular visual exposure of the same duration. The results of longitudinal measurements of acuity made on one of these animals (C337) that exhibited the best recovery is displayed in figure 26. It is apparent from the results of all ten monocularly deprived animals that subsequently received only successive (as opposed to simultaneous) visual experience with the two eyes that this procedure does not lead to recovery of good vision in either eye. This was so even if each eye obtained the same daily visual exposure as did the two eyes of kittens that received a period of daily simultaneous visual experience with both eyes, and which recovered normal visual acuities as a result.

### (*d*) *Full-time followed by part-time reverse occlusion*

Because the substantial recovery in the vision of the initially deprived eye that is achieved during a period of full-time reverse occlusion typically is not maintained afterwards during a period of exclusive binocular visual exposure, a preliminary exploration was made of the effects of interposing a period of part-time reverse occlusion between the two. This particular procedure was investigated on three animals, one of which had been monocularly deprived to six weeks old whereas the other two were deprived initially to eight weeks. Each animal was subsequently subjected to a four-week to six-week period of effectively full-time reverse occlusion, during which time the initially non-deprived eye was occluded with a helmet for all 7 h of daily visual exposure (see table 3). Following this period, the animals received a regimen of part-time reverse occlusion for the next 22–26 days, during which time the initially non-deprived eye was occluded for only 3.5 h each day. At the end of this period the animal received exclusively binocular visual input for all 7 h of daily visual exposure. The results of longitudinal measurements of the acuity of the two eyes of all three animals are shown in figure 27. It was readily apparent that the introduction of a period of part-time reverse occlusion immediately following full-time occlusion failed to maintain the acuity of the initially deprived eye at the (high) level it had attained during the latter period. This point was particularly

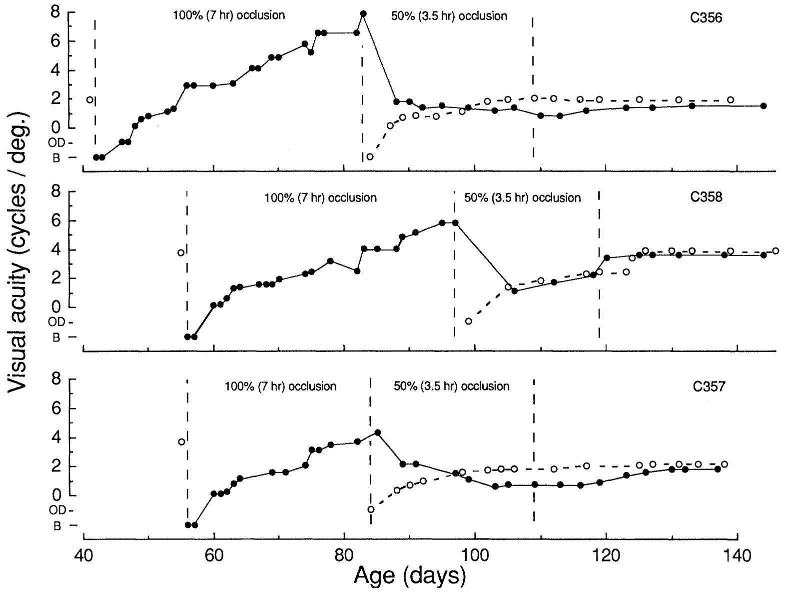

Figure 27. Longitudinal measurements of the visual acuities of the two eyes of three animals that had been monocularly deprived to six weeks old, and which had then received a period of full-time reverse occlusion followed by a period of part-time reverse occlusion in which the initially non-deprived eye was occluded for 3.5 h each day. Symbols and abbreviations are as for figure 2. All three animals developed bilateral amblyopia.

evident in the data for C356, the only animal that was monocularly deprived to six weeks old and which, as a consequence, exhibited the greatest degree of visual recovery in its initially deprived eye during the subsequent period of full-time reverse occlusion. At the end of the latter period, the initially deprived eye of this animal had attained an acuity (7.8 cycles deg$^{-1}$) that was within the range of values observed in normal animals. Nevertheless, within four days of introduction of the part-time reverse occlusion regimen the acuity of this eye had dropped to only 1.80 cycles deg$^{-1}$, after which it changed very little. A similar rapid drop in the acuity of the initially deprived eye was observed with the other two animals. During the short period of part-time reverse occlusion the acuity of the other eye improved gradually to a level that was equal to, or only slightly greater than, that of the initially deprived eye at the end of this period. Interestingly, there was very little change in the acuity of either eye following termination of the period of part-time reverse occlusion. In every animal the final outcome was severe bilateral amblyopia.

## DISCUSSION

### (*a*) *The basis of performance on the behavioural task*

Before a discussion of the various results of this study and their possible physiological substrates, it is appropriate to comment on the various factors that may limit performance on the grating-detection task that was employed. Although performance on such a task can be limited solely by a true sensory deficit that reflects physiological changes induced in the visual pathway by the various occlusion regimens examined, it can also be affected by associated optical or oculomotor abnormalities that may either be induced directly by the various deprivation regimens, or else arise indirectly as a consequence of the sensory deficit.

One or both of two oculomotor anomalies, namely strabismus and nystagmus, have been reported occasionally in the past in kittens (Sherman 1972; Blake *et al.* 1974; Olson & Freeman 1978*b*; Cynader 1979; Kaye *et al.* 1982; Mitchell 1988) and monkeys (Regal *et al.* 1976; Sparks *et al.* 1986; Sloper *et al.* 1988; Quick *et al.* 1989; Tusa *et al.* 1991) following various forms of early monocular or binocular deprivation. Although quantitative measurements of eye alignment were not made on the animals reported on here, some animals did appear to possess a strabismus; it is therefore possible that any reduction in the vision of one eye of such an animal could be attributed to the onset of strabismic amblyopia. However, as argued earlier (Mitchell *et al.* 1984*b*), it is extremely unlikely that the visual loss observed in the initially deprived eye can always be explained in such terms in view of the time course of the acuity changes that are observed and the ages at which they can be observed. Moreover, as strabismic amblyopia occurs in just one eye (usually the eye that habitually deviates) it is difficult to explain the frequent observation of severe bilateral amblyopia following termination of reverse occlusion in such terms. Finally, the lack of any obvious relation between the presence of strabismus and amblyopia is emphasized by the fact that certain animals (such as C115) that did manifest a strabismus that was evident on casual inspection, or the four kittens on which an optical strabismus was imposed, all developed good visual acuity in both eyes.

Although a pendular nystagmus was observed in both eyes of only one animal of this study it is possible that tremors of smaller amplitude and/or higher velocity that would escape detection by the naked eye were present in many more animals. Without sensitive methods for monitoring eye movements (such as the use of search coils) it is not possible to estimate the frequency of occurrence of nystagmus, which could undoubtedly reduce performance on the grating-acuity task. Even if nystagmus were found in an appreciable proportion of animals that developed amblyopia in one or both eyes, the nature of any link between the two would still be uncertain. At one extreme the nystagmus could be the primary deficit that by itself could explain most if not all of the acuity loss, whereas at the other extreme the nystagmus may follow as a consequence of a sensory loss and contribute little or nothing to the measured visual deficit.

The remaining optical or oculomotor factors that could contribute to the visual deficits observed in this study are refractive or accommodative errors that may be induced by the complex deprivation regimens used in this study. However, retinoscopy revealed no substantial refractive errors in any of the animals, and it is very unlikely that any accommodative error could degrade grating acuity at the observation distance (usually 70 cm) typically used for the latter stages of the behavioural tests.

Because of the lack of any compelling evidence to the contrary, it is necessary to assume that the substantial amblyopia observed in one or both eyes of the animals of this study can be attributed to changes in the geniculo-cortical pathway, particularly at levels central to the lateral geniculate nucleus. Attempts to provide explanations for the origin of the deficits in acuity associated with monocular deprivation have frequently been sought in terms of the substantial shifts in the ocular dominance of cortical cells associated with this form of early visual deprivation. However, as has been pointed out previously (see, for example, Mitchell *et al.* 1977*a*; Blakemore 1988), it is likely that acuity would be correlated more with the spatial properties of individual cortical cells driven through a given eye than the mere fraction of the total population of cells that are dominated by that eye. Indeed, clear evidence of a dissociation between the extent of shifts in ocular dominance of cortical cells induced by various forms of early visual deprivation and the changes in the spatial performance of the cells influenced by the two eyes, or else the acuity of the two eyes, have been reported in a number of studies (Hirsch *et al.* 1987; Blakemore 1988; Freeman & Ohzawa 1988; Mitchell & Cynader, unpublished observations). However, although an index of the strength of connections of cortical cells with a given eye, such as ocular dominance, may not always predict the nature of the spatial characteristics of the centre mechanism of the cells driven by that eye (and hence their spatial resolution), it is possible that the two may be correlated in certain extreme situations.

### (*b*) *Full-time reverse occlusion*

The additional rearing conditions studied here provide further confirmation of the various outcomes observed in earlier studies (Mitchell *et al.* 1984*a*, *b*; Murphy & Mitchell 1987) that examined the eventual consequences of a more restricted set of regimens of reverse occlusion. However, more importantly, they point to both the infrequent circumstances in which a beneficial final outcome is observed where both eyes achieve good visual acuity (figure 1) and the wide spectrum of exposure conditions that lead eventually to bilateral amblyopia (figure 6).

Included among the rearing conditions examined were a further set of extreme situations similar to one explored in a previous study (Murphy & Mitchell 1987) that would be thought to permit the good vision gained by the initially deprived eye during reverse occlusion to be maintained afterwards. Such an outcome might be expected to occur if reverse occlusion were imposed early in life and for a long period of time, so that binocular visual input would be introduced near the end of known sensitive periods in development of the central visual pathways. In the earlier study it had been shown that even when reverse occlusion was imposed at four weeks old for 12 weeks, the acuity of the initially deprived eye dropped rapidly in the first few days following introduction of binocular visual input. However, as shown in figure 2, the acuity of this eye remained high in an animal (C392) that was reverse-occluded for the same length of time but slightly earlier, at 25 days old. And as indicated by the three animals of figure 3, a similar outcome was observed in animals that had also been monocularly deprived to four weeks old but reverse-occluded for much longer periods (16–24 weeks). Thus it would appear that periods of reverse occlusion of four months or more can permanently reverse the visual deficits shown by the deprived eye of animals monocularly deprived to four weeks old. Of course, although the visual acuity of the initially deprived eye may be normal, the vision of the other eye is extremely poor (figures 2 and 6). A similar observation was made on two animals in the single published study of the permanence of the behavioural effects of reverse occlusion imposed on monocularly deprived monkeys (Harwerth *et al.* 1989). These particular animals, which were reverse-occluded for 120 days after either a 14-day or 30-day period of monocular deprivation imposed at 22–34 days old, exhibited contrast-sensitivity functions within the normal range for the initially deprived eye but only rudimentary vision with the other eye.

As illustrated by figures 6 and 7, by far the most common final outcome following termination of full-time reverse occlusion was the condition of bilateral amblyopia. Although in some cases the vision of one eye was superior to the other, the acuity of the better eye was still subnormal. Although only very limited data exist on monkeys, there is good evidence that a similar eventual outcome is observed following certain regimens of reverse occlusion in this species. One of the four monkeys (subject V) examined by Harwerth *et al.* (1989), which was reverse-occluded for 120 days after 90 days of monocular deprivation that began at between three and four weeks old, showed reduced contrast sensitivities in both eyes that were particularly noteworthy at high spatial frequencies. In a study of the effects of reverse occlusion on cell size in the monkey lateral geniculate nucleus, Sloper *et al.* (1988) conducted some crude tests of visual function in a number of their monocularly deprived animals that had short periods (9–36 days) of reverse occlusion imposed at 22 days old. One or two animals (OM 446) that received only nine days of reverse occlusion developed severe bilateral nystagmus and appeared to have no useful vision on the basis of casual tests. The other animal developed a divergent strabismus of variable angle and appeared to fixate with its initially non-deprived eye. Although no formal tests were conducted, the other eye appeared to have poor vision. Similar short periods of reverse occlusion (nine days), when imposed on monocularly deprived kittens at four weeks old, were shown in a previous study to result reliably in severe bilateral amblyopia (Murphy & Mitchell 1987). Finally, the five monkeys described very recently by Tusa *et al.* (1991) that were initially monocularly deprived from birth to 25 days old before an identical period of reverse occlusion all subsequently developed bilateral amblyopia, although the amblyopia was more severe in the initially deprived eye. In addition, each animal manifested an exotropia as well as either monocular (the initially deprived eye of cynomolgus monkeys) or binocular (rhesus monkeys) pendular nystagmus.

Whatever the final result, whether it was unilateral or bilateral amblyopia, or even the rare situation where good vision was recovered in both eyes, one of the most reliable observations on termination of a period of reverse occlusion was a rapid loss of vision in the initially deprived eye that in some situations was temporary but in most was permanent. Although the rapid loss of vision in this eye was accompanied by an improvement in the vision of the initially non-deprived eye, the latter changes often occurred at a substantially slower speed. This point was particularly evident following rearing situations examined in earlier papers (figures 1 and 4 of Mitchell *et al.* (1984*b*), figures 6 and 8 of Murphy & Mitchell (1987)) and in data from animals, such as those of figure 2, that were reverse-occluded for long periods of time. Frequently in such situations the vision of the initially deprived eye had dropped to its final level long before any signs of vision were evident in the newly opened other eye. This asymmetry suggests that the functional loss of vision in the initially deprived eye is not a consequence of an underlying homeostatic mechanism that maintains the overall functional input from the two eyes at a constant level. Recent chronic recordings from implanted floating microelectrodes in the kitten visual cortex during monocular deprivation and reverse occlusion provide evidence of a parallel asymmetry in terms of shifts of ocular dominance (Mioche & Singer 1989). After reverse occlusion, the first change to be observed was a reduction in the response of cells to visual stimulation of the newly deprived (initially non-deprived) eye, followed much later by the reappearance of a response in the initially deprived eye. Sometimes the latter was not observed before the former had disappeared.

The fact that very similar phenomena were observed (figure 5) following termination of a period of reverse occlusion in animals that received either four or five weeks of normal visual exposure before monocular deprivation and in those that were so deprived from birth, suggests that these events are not a consequence of the exclusively early monocular vision of the latter. In particular, these findings argue against the simple notion that the functional connections established first with one or both eyes in early postnatal life are in some way more robust than those established later. Ignoring for the moment the mechanism by which this could occur, the drop in the vision of the initially deprived eye observed after termination of reverse occlusion in animals that had been monocularly deprived from birth might reflect a competitive advantage of the functional connections that were established first. However, the fact that similar results were observed in animals that received a prior period of normal vision argues against this simple interpretation and instead suggests that the phenomena are a consequence of events established during the initial period of monocular deprivation, whether or not it is preceded by normal visual exposure.

An interesting recent observation by Reiter & Stryker (1988) points to a possible mechanism that may account for the rapid loss of vision in the initially deprived eye following termination of certain regimens of reverse occlusion. Selective blocking of visual-cortical-cell action potentials by continuous infusion of muscimol during monocular deprivation was found to lead to a shift of ocular dominance towards the less active, deprived eye. On the basis of this finding, Reiter & Stryker proposed a modified 'learning rule' for ocular dominance plasticity, namely that connections between active, non-deprived eye inputs and the postsynaptic cell are weakened relative to inputs from the deprived eye when the cell is strongly inhibited, whereas the reverse is true when the cell is not inhibited. In a sense this rule proposes the existence of a threshold membrane potential that determines the direction of an ocular dominance shift. There is a body of evidence that suggests that weak subthreshold functional connections to cortical cells from the deprived eye remain after even extended periods of monocular deprivation (see, for example, Fiorentini & Maffei 1979; Blakemore *et al.* 1982; Freeman & Ohzawa 1988) and that inhibitory connections (possibly mediated by intrinsic interneurons) may be more resistant to visual deprivation than are excitatory connections (see, for example, Singer 1977; Mioche & Singer 1989). It is possible that, under certain restricted conditions of monocular deprivation, reverse occlusion and subsequent introduction of binocular visual input, inhibitory influences from the newly opened (initially non-deprived) eye may sufficiently inhibit cortical cells to lead to a weakening of responses from the more active (initially deprived) eye, by virtue of the operation of a rule similar to that proposed by Reiter & Stryker (1988).

### (*c*) ***Part-time reverse occlusion***

Perhaps the most interesting finding to emerge from these particular studies was the effectiveness of certain occlusion regimens in animals that were monocularly deprived to as late as 10 weeks old. Although two occlusion regimens (3.5 and 5 h) permitted recovery of good vision in both eyes of animals monocularly deprived to six weeks old, only the second of these conditions proved successful in animals deprived for longer periods. Finally, in animals deprived to 12 weeks old, even this condition proved to be ineffective.

During the time that part-time reverse occlusion was imposed, there was a progressive increase in the acuity achieved by the initially deprived eye with increasing amounts of daily occlusion of the other eye (figures 11 and 18). In this respect the findings were in accordance with conventional clinical guidelines for treatment of amblyopia that emphasize constant occlusion of the non-amblyopic eye (see, for example, Duke-Elder & Wybar 1973; Von Noorden 1980). However, in contrast to the changes that occurred during the period of occlusion, the subsequent changes in the vision of the two eyes bore no simple relation to the amount of time the initially non-deprived eye had been occluded each day. Both short and long periods of daily occlusion led to poor vision in one or both eyes, whereas certain intermediate occlusion times resulted in the eventual attainment of normal visual acuities in both eyes. Because all the experiments used the same total daily period of visual exposure (7 h), it was not possible to identify whether the important variable was the number of hours of daily occlusion (i.e. 3.5 or 5 h) or the proportion (50% or 70%) of the total daily period of visual exposure that this occlusion occupied. However, the comparable final outcome observed in the single animal on which a variant of one of these occlusion regimens was instituted (figure 15) provides some limited support for the latter interpretation.

Although it is only possible to speculate at this point on possible mechanisms that might underlie the beneficial behavioural outcome associated with certain regimens of part-time reverse occlusion, some parallels exist with the findings of two physiological studies. A prior hint of the beneficial consequence of daily periods of binocular visual exposure was given in a study by Olson & Freeman (1980), who found that the dramatic effects on cortical ocular dominance of 4 h daily periods of monocular deprivation could be eliminated completely if the animals received binocular visual input for the rest of the day. In addition, the finding that visual recovery occurs in the presence of discordant visual input during the daily periods of binocular visual exposure (figure 23) is paralleled closely by the results of a recent physiological study (Malach & Van Sluyters 1989) of recovery from monocular deprivation in the presence of a strabismus introduced by surgical means immediately following termination of the period of monocular occlusion. The recovery of ocular dominance in these animals was no different from that observed in the usual situation, a finding that is incompatible with simple Hebbian models of synaptic modification and particularly those that propose a role for postsynaptic action potentials in synaptic modification (Hebb 1949; Stent 1973; Movshon & Van Sluyters 1981).

Because the visual axes may not have always been aligned following the period of part-time reverse occlusion (Blake *et al.* 1974), it is possible that a significant misalignment of the two eyes was present in many animals throughout the daily period of binocular visual exposure. In such a case the vertical misalignment of the visual axes introduced by the prisms in this period may have simply added to a strabismus that was already present. Consequently the external manipulation (the introduction of prisms) did not alter in an appreciable manner the situation that must have existed in many of the animals in which good recovery of vision had been observed. Alternatively, it is possible that good visual recovery was possible in the presence of prism-induced optical misalignment because the degree of vertical misalignment was only modest, so that Hebbian or other synaptic modification rules could operate on binocular cells with large receptive fields. Although the rules of synaptic modification that permit good recovery of vision in the presence of vertical misalignment of the visual axes remain elusive, it is of interest that even smaller degrees of vertical misalignment (8 prism-dioptres) have been shown to be sufficient to disrupt cortical binocularly as assessed by simple measures of ocular dominance (Van Sluyters & Levitt 1980). Thus it can be concluded that the synaptic rule responsible for the breakdown of cortical binocularity in the presence of vertical misalignment of the visual axes must be different from that responsible for the synaptic mechanisms that underlie the changes in the visual acuity in the two eyes.

The monocularly deprived animals on which several regimens of sequential rather than simultaneous daily periods of exposure of the two eyes were imposed all developed severe bilateral amblyopia (figures 24–26). Thus, on the basis of these observations and the previous experiment with prisms, it is apparent that for recovery to occur in response to part-time reverse occlusion it is necessary for the two eyes to receive approximately simultaneous visual input each day, but it is not necessary for the visual input in this period to be strictly concordant. The severity of the bilateral amblyopia associated with those occlusion regimens that incorporated sequential exposure of the two eyes was surprising. Although previous experiments on the consequences of alternating monocular deprivation (Hubel & Wiesel 1965) would predict that such rearing conditions would reduce the proportion of binocularly excitable cells and that unequal exposures of the two eyes would lead to a corresponding imbalance in the proportion of cells dominated by each eye (Tieman *et al.* 1983), none of the previous physiological studies would have predicted the behavioural effects that were observed.

Finally, it is important to emphasize the variety of different eventual outcomes that occurred in response to the varied conditions of monocular deprivation and subsequent regimens of part-time or full-time reverse occlusion that were examined. As illustrated by figures 6 and 7, which summarized the data from only full-time reverse occlusion, these include conditions of unilateral or bilateral amblyopia of varying severity, as well as good vision in both eyes in certain very restricted circumstances. As these experiments were all behavioural in nature, it is possible only to speculate on possible reasons for the variety of observed outcomes and the restricted set of conditions under which they occur. However, the evidence for competitive interactions in development between *X* and *Y* pathways, as well as for different sensitive periods in their development, provide a potentially profitable avenue to explore (Garraghty *et al.* 1986).

### (*d*) *Clinical relevance and implications*

The reverse-occlusion regimens studied represent only a subset of those used clinically for the treatment of the various identified forms of human amblyopia. Because the initial period of monocular deprivation employed here mimics the presumed precipitating cause of deprivation amblyopia (deprivation of pattern vision) in humans, the various reverse-occlusion regimens that were studied are perhaps most relevant to the treatment of this particular form of human amblyopia. The major difference between the occlusion regimens examined here and those used clinically is the developmental age at which they are initiated. Even when the substantial differences in the durations of known sensitive periods in visual development in the two species are taken into account (Mitchell & Timney 1984), it is apparent that the ages at which human amblyopic infants typically first receive occlusion therapy are considerably later than the equivalent ages of the kittens when the various reverse-occlusion regimens were initiated in this study. However, despite this difference there is already a body of evidence that suggests that certain of the outcomes observed in the kittens of this study are also observed clinically. For example, the labile nature of the recovery produced by certain full-time regimens of reverse occlusion finds close parallels in a number of clinical reports (see, for example, von Noorden 1969, 1985), including some recent studies on very young infants (see, for example, Jacobson *et al.* 1981, 1983). Fortunately, many of the occlusion conditions that resulted in bilateral amblyopia in the kittens of this study were unlikely to have occurred in a clinical context until comparatively recent times, with the increasing tendency for earlier treatment. Virtually all the rearing situations that resulted in bilateral amblyopia involved full-time occlusion. This practice is difficult to achieve with infants, with the result that occlusion is almost always part-time.

Because of the growing tendency for early treatment of all forms of amblyopia, including the use of aggressive occlusion regimens, the potential for the subsequent development of bilateral amblyopia has certainly been increased. However, the successful visual recovery achieved in monocularly deprived kittens following certain regimens of part-time reverse occlusion, together with recent reports of similar successful outcomes among infants with deprivation amblyopia (associated with monocular congenital cataracts) following close compliance with comparable part-time occlusion regimens (Tytla *et al.* 1988; Birch & Stager 1988; Drummond *et al.* 1989), indicates a route by which the development of bilateral amblyopia can be successfully avoided.

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## REFERENCES

Baker, F. H., Grigg, P. & von Noorden, G. K. 1974 Effects of visual deprivation and strabismus on the response of neurons in the visual cortex of the monkey, including studies on the striate and prestriate cortex in the normal animal. *Brain Res.* **66**, 185–208.

Berkley, M. A. 1981 Animal models of visual development: behavioral evaluation of some physiological findings in cat visual development. In *Development of perception*, vol. 2. *The visual system* (ed. R. N. Aslin, J. R. Alberts & M. R. Peterson), pp. 197–215. New York: Academic Press.

Birch, E. E. & Stager, D. R. 1988 Prevalence of good visual acuity following surgery for congenital unilateral cataract. *Arch. Ophthalmol.* **106**, 40–43.

Blake, R., Crawford, M. L. J. & Hirsch, H. V. B. 1974 Consequences of alternating monocular deprivation on eye alignment and convergence in cats. *Invest. Ophthalmol.* **13**, 121–126.

Blakemore, C. 1988 The sensitive periods of the monkey's visual cortex. In *Strabismus and amblyopia. Experimental basis for advances in clinical management* (ed. G. Lennerstrand, G. K. von Noorden & E. C. Campos), pp. 219–234. London: Plenum Press.

Blakemore, C., Garey, L. J. & Vital-Durand, F. 1978 The physiological effects of monocular deprivation and their reversibility in the monkey's visual cortex. *J. Physiol., Lond.* **283**, 223–262.

Blakemore, C., Hawken, M. J. & Mark, R. F. 1982 Brief monocular deprivation leaves subthreshold synaptic input on neurones of the cat's visual cortex. *J. Physiol., Lond.* **327**, 489–505.

Blakemore, C. & Van Sluyters, R. C. 1974 Reversal of the physiological effects of monocular deprivation in kittens: further evidence for a sensitive period. *J. Physiol., Lond.* **237**, 195–216.

Blakemore, C., Vital-Durand, F. & Garey, L. J. 1981 Recovery from monocular deprivation in the monkey. I. Recovery of physiological effects in the visual cortex. *Proc. R. Soc. Lond.* B **213**, 399–423.

Bradley, A. & Freeman, R. D. 1985 Is reduced vernier acuity in amblyopia due to position, contrast or fixation deficits? *Vis. Res.* **25**, 55–66.

Crawford, M. L. J., de Faber, J. T., Harwerth, R. S., Smith, E. L. & von Noorden, G. K. 1989 The effects of reverse monocular deprivation in monkeys. II. Electrophysiological and anatomical studies. *Expl Brain Res.* **74**, 338–347.

Cynader, M. 1979 Interocular alignment following visual deprivation in the cat. *Invest. Ophthal. vis. Sci.* **18**, 726–741.

Dews, P. B. & Wiesel, T. N. 1970 Consequences of monocular deprivation on visual behaviour in kittens. *J. Physiol., Lond.* **206**, 437–455.

Drummond, G. T., Scott, W. E. & Keech, R. V. 1989 Management of monocular congenital cataracts. *Arch. Ophthalmol.* **107**, 45–51.

Duke-Elder, S. & Wybar, K. 1973 *System of ophthalmology*, vol. 6. *Ocular motility and strabismus*, pp. 424–425. London: Kimpton.

Dzioba, H. A., Murphy, K. M., Horne, J. A. & Mitchell, D. E. 1986 A precautionary note concerning the use of contact lens occluders in developmental studies on kittens, together with a description of an alternative occlusion procedure. *Clin. Vis. Sci.* **1**, 191–196.

Fiorentini, A. & Maffei, L. 1979 Responses of cortical neurones of monocularly deprived kittens: a re-examination. *J. Physiol., Lond.* **291**, 35*P*.

Freeman, R. D. & Ohzawa, I. 1988 Monocularly deprived cats: binocular tests of cortical cells reveal functional connections from the deprived eye. *J. Neurosci.* **8**, 2491–2506.

Garraghty, P. E., Sur, M. & Sherman, S. M. 1986 Role of competitive interactions in the postnatal development of *X* and *Y* retinogeniculate axons. *J. comp. Neurol.* **251**, 216–239.

Giffin, F. & Mitchell, D. E. 1978 The rate of recovery of vision after early monocular deprivation in kittens. *J. Physiol., Lond.* **274**, 511–537.

Harwerth, R. S., Smith, E. L., Crawford, M. L. J. & von Noorden, G. K. 1989 The effects of reverse monocular deprivation in monkeys. I. Psychophysical experiments. *Expl Brain Res.* **74**, 327–337.

Hebb, D. O. 1949 *The organization of behavior*. New York: John Wiley.

Hirsch, H. V. B., Tieman, D. G., Tieman, S. B. & Tumosa, N. 1987 Unequal alternating exposure: effects during and after the classical critical period. In *Imprinting and cortical plasticity* (ed. J. P. Rauschecker & P. Marler), pp. 287–320. New York: John Wiley.

Hubel, D. H. & Wiesel, T. N. 1965 Binocular interaction in striate cortex of kittens reared with artificial squint. *J. Neurophysiol.* **28**, 1041–1059.

Hubel, D. H., Wiesel, T. N. & Levay, S. 1977 Plasticity of ocular dominance columns in monkey striate cortex. *Phil. Trans. R. Soc. Lond.* B **278**, 377–409.

Jacobson, S. G., Mohindra, I. & Held, R. 1981 Development of visual acuity in infants with congenital cataracts. *Br. J. Ophthalmol.* **65**, 727–735.

Jacobson, S. G., Mohindra, I. & Held, R. 1983 Monocular form deprivation in human infants. *Docum. Ophthalmol.* **55**, 199–211.

Kaye, M., Mitchell, D. E. & Cynader, M. 1982 Depth perception, eye alignment and cortical ocular dominance of dark-reared cats. *Devl Brain Res.* **2**, 37–53.

Levay, S., Wiesel, T. N. & Hubel, D. H. 1980 The development of ocular dominance columns in normal and visually deprived monkeys. *J. comp. Neurol.* **191**, 1–51.

Malach, R. & Van Sluyters, R. C. 1989 Strabismus does not prevent recovery from monocular deprivation: a challenge for simple Hebbian models of synaptic modification. *Vis. Neurosci.* **3**, 267–273.

Mioche, L. & Singer, W. 1989 Chronic recordings from single sites of kitten striate cortex during experience-dependent modifications of receptive-field properties. *J. Neurophysiol.* **62**, 185–197.

Mitchell, D. E. 1988 The extent of visual recovery from early monocular or binocular visual deprivation in kittens. *J. Physiol., Lond.* **395**, 639–660.

Mitchell, D. E. 1989 Sensitive periods in visual development in the kitten: the effects of early monocular deprivation. In *Problems and concepts in developmental neurophysiology* (ed. P. Kellaway & J. L. Noebels), pp. 45–74. Baltimore: Johns Hopkins University Press.

Mitchell, D. E., Cynader, M. & Movshon, J. A. 1977*a* Recovery from the effects of monocular deprivation in kittens. *J. comp. Neurol.* **176**, 53–64.

Mitchell, D. E., Giffin, F. & Timney, B. 1977*b* A behavioural technique for the rapid assessment of the visual capabilities of kittens. *Perception* **6**, 181–193.

Mitchell, D. E., Murphy, K. M., Dzioba, H. A. & Horne, J. A. 1986 Optimization of visual recovery from early monocular deprivation in kittens: implications for occlusion therapy in the treatment of amblyopia. *Clin. Vis. Sci.* **1**, 173–177.

Mitchell, D. E., Murphy, K. M. & Kaye, M. 1984*a* Labile nature of the visual recovery promoted by reverse occlusion in monocularly deprived kittens. *Proc. natn. Acad. Sci. U.S.A.* **81**, 286–288.

Mitchell, D. E., Murphy, K. M. & Kaye, M. G. 1984*b* The permanence of the visual recovery that follows reverse occlusion of monocularly deprived kittens. *Invest. Ophthal. vis. Sci.* **25**, 908–917.

Mitchell, D. E. & Timney, B. 1984 Postnatal development of function in the mammalian visual system. In *Handbook of physiology*, section I: *The nervous system*, vol. 3, part 1. *Sensory processes* (ed. I. Darian-Smith), pp. 507–555. Bethesda: American Physiological Society.

Movshon, J. A. 1976*a* Reversal of the physiological effects of monocular deprivation in the kitten's visual cortex. *J. Physiol., Lond.* **261**, 125–174.

Movshon, J. A. 1976*b* Reversal of the behavioural effects of monocular deprivation in the kitten. *J. Physiol., Lond.* **261**, 175–188.

Movshon, J. A. & Van Sluyters, R. C. 1981 Visual neural development. *A. Rev. Psychol.* **32**, 477–522.

Murphy, K. M. & Mitchell, D. E. 1986 Bilateral amblyopia following a short period of reverse occlusion in kittens. *Nature, Lond.* **323**, 536–538.

Murphy, K. M. & Mitchell, D. E. 1987 Reduced visual acuity in both eyes of monocularly deprived kittens following a short or a long period of reverse occlusion. *J. Neurosci.* **7**, 1526–1536.

Murphy, K. M. & Mitchell, D. E. 1991 Vernier acuity of normal and visually deprived cats. *Vis. Res.* **31**, 253–266.

Olson, C. R. & Freeman, R. D. 1978*a* Monocular deprivation and recovery during sensitive period in kittens. *J. Neurophysiol.* **41**, 65–74.

Olson, C. R. & Freeman, R. D. 1978*b* Eye alignment in kittens. *J. Neurophysiol.* **41**, 848–859.

Olson, C. R. & Freeman, R. D. 1980 Cumulative effects of brief daily periods of monocular vision on kitten striate cortex. *Expl Brain Res.* **38**, 53–56.

Quick, M. W., Tigges, M., Gammon, J. A. & Boothe, R. G. 1989 Early abnormal visual experience induces strabismus in infant monkeys. *Invest. Ophthal. vis. Sci.* **30**, 1012–1017.

Regal, D., Boothe, R., Teller, D. Y. & Sacket, G. B. 1976 Visual acuity and visual responsiveness in dark-reared monkeys (*Macaca nemestrina*). *Vision Res.* **16**, 523–530.

Reiter, H. O. & Stryker, M. P. 1988 Neural plasticity without synaptic action potential: less-active inputs become dominant when kitten visual cortical cells are pharmacologically inhibited. *Proc. natn. Acad. Sci. U.S.A.* **85**, 3623–3627.

Sherman, M. 1972 Development of interocular alignment in cats. *Brain Res.* **37**, 187–203.

Shimojo, S., Birch, E. E., Gwiazda, J. & Held, R. 1984 Development of vernier acuity in infants. *Vis. Res.* **24**, 721–728.

Singer, W. 1977 Effects of monocular deprivation on excitatory and inhibitory pathways in cat striate cortex. *Expl Brain Res.* **30**, 25–41.

Sloper, J. J., Headon, M. P. & Powell, T. P. S. 1988 Experiments to study recovery of LGN cell size following monocular lid closure and reverse suture in infant monkeys. *Devl Brain Res.* **40**, 47–59.

Smith, D. C. & Holdefer, R. N. 1985 Binocular competitive interaction and recovery of visual acuity in long-term monocularly deprived cats. *Vis. Res.* **25**, 1783–1794.

Sparks, D. L., Gurski, M. R., Mays, L. E. & Hickey, T. L. 1986 Effects of long-term and short-term monocular deprivation upon oculomotor functions in the rhesus monkey. In *Adaptive processes in visual and oculomotor systems* (ed. E. L. Keller & D. S. Zee), pp. 191–197. Oxford: Pergamon Press.

Stent, G. S. 1973 A physiological mechanism for Hebb's postulate of learning. *Proc. natn. Acad. Sci. U.S.A.* **70**, 997–1001.

Swindale, N. V., Vital-Durand, F. & Blakemore, C. 1981 Recovery from monocular deprivation in the monkey. III. Reversal of anatomical effects in the visual cortex. *Proc. R. Soc. Lond.* B **213**, 435–450.

Tieman, D. G., McCall, M. A. & Hirsch, H. V. B. 1983 Physiological effects of unequal alternating monocular exposure. *J. Neurophysiol.* **49**, 804–818.

Tusa, R. J., Repka, M. X., Smith, C. B. & Herdman, S. J. 1991 Early visual deprivation results in persistent strabismus and nystagmus in monkeys. *Invest. Ophthal. vis. Sci.* **32**, 134–141.

Tytla, M. E., Maurer, D., Lewis, T. L. & Brent, H. P. 1988 Contrast sensitivity in children treated for congenital cataract. *Clin. Vis. Sci.* **2**, 251–264.

Van Sluyters, R. C. & Levitt, F. B. 1980 Experimental strabismus in the kitten. *J. Neurophysiol.* **43**, 686–699.

von Noorden, G. K. 1969 The etiology and pathogenesis of fixation anomalies in strabismus. *Trans. Am. ophthal. Soc.* **67**, 698–751.

von Noorden, G. K. 1980 *Binocular vision and ocular motility*, 2nd edn, pp. 436–437. St Louis, Missouri: Mosby.

von Noorden, G. K. 1985 Idiopathic amblyopia. *Am. J. Ophthalmol.* **100**, 214–217.

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