THE POSTNATAL DEVELOPMENT OF THE VISUAL CORTEX AND THE INFLUENCE OF ENVIRONMENT

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INTRODUCTION

In the early sixties, having begun to describe the physiology of cells in the adult cat visual cortex, [1] David Hubel and I decided to investigate how the highly specific response properties of cortical cells emerged during postnatal development. We were also interested in examining the role of visual experience in normal development, a question raised and discussed by philosophers since the time of Descartes. The design of these experiments was undoubtedly influenced by the observation that children with congenital cataract still have substantial and often permanent visual deficits after removal of the cataract and proper refraction. [2] Also, behavioral studies had shown that animals raised in the dark or in an environment devoid of contours have a similar impairment of their visual functions. [3,4]

Because of the difficulties associated with raising kittens in total darkness, we decided to fuse the lids by suture. This procedure prevented any form vision without completely depriving the animal of light. We expected this to be an effective procedure because cortical cells respond to contours and are insensitive to changes in levels of diffuse light. [5] Initially we raised kittens with only one eye closed, using the other eye as a control. This design turned out to be fortunate, because - as shown below - the effects of single eye closure on the visual cortex are more dramatic than the results obtained from animals raised with both eyes occluded or kept in the dark.

Our initial findings were that kittens with one eye occluded by lid suture during the first three months of life were blind in the deprived eye, and that in the striate cortex the majority of the cells responded only to stimulation of the normal eye. [6] This defect appeared to be localized to the visual cortex, perhaps at the site of interaction between geniculate afferents and cortical cells. [7] From another series of experiments, we found that the properties of orientation specificity and binocularity developed through innate mechanisms. [8] This result, taken together with the monocular deprivation experiment, indicated that neural connections present early in life can be modified by visual experience.

Such neural plasticity was not observed in the adult cat, but existed only during the first three postnatal months. [9]

The early experiments were done in the cat, but we soon turned our attention to the rhesus macaque monkey. After having demonstrated that cells in the monkey visual cortex also respond selectively to lines of different orientations and often are binocular [10] we showed that the monkey was also susceptible to visual deprivation, [11] a finding subsequently confirmed and extended. [12, 13, 14, 15] Further advances in our understanding of the nature of and mechanism underlying the deprivation phenomena depended on working out some of the functional architecture of the visual cortex. This was done through further physiological experiments in the normal animal and by using newly developed anatomical methods. [16, 17, 18, 19, 20] Over the years we have pursued the normal and developmental studies in parallel, and this has accelerated our progress in both areas. For example, while the deprivation experiments depended on the understanding of the functional architecture of the normal adult animal, we were alerted to the existence of ocular dominance columns in the cat by experiments we had done in strabismic animals. [21]

In this lecture I will present our current understanding of the development of the monkey visual cortex and the role of visual experience in influencing neural connections. Rather than attempting to discuss in any detail the now very extensive literature in the field, my emphasis will be on the work carried out in our laboratory (for reviews see references 22, 23 and 24). David Hubel and I did much of this work in collaboration with Simon LeVay.

MONOCULAR DEPRIVATION

The procedure of suturing a monkey's eyelid shut creates a condition similar to a cataract, since though the light reaching the retina through the closed lid is only slightly attenuated (by factor of 3), the forms of objects are no longer visible. As mentioned above, when the deprived eye is opened after months of deprivation, the animal is unable to see with it; there are no obvious changes in the ocular media, the retina or the LGN that can explain this deficit; instead marked changes have occurred at the level of the primary visual cortex (striate cortex). Even if the ocular media are clear, the occluded eye develops with time a marked axial length myopia (5-12 D over a 1 year period). [25]

One way of seeing the change is to record from cells in the striate cortex and determine their ocular preference. [7] In the monkey there is normally a fairly even balance between cells driven preferentially by one eye and cells driven preferentially by the other. [10] In layer IV most cells are strictly monocular, and outside of layer IV they are usually binocular, though they still tend to respond more strongly to stimulation of one eye than to the other. There are about as many cells preferring stimulation of the left eye as cells preferring stimulation of the right (Fig. 1, left). Under conditions of monocular deprivation, however, the great majority of cortical cells are driven exclusively by the nondeprived eye (Fig. 1, right). [11, 12, 13] One could ask whether this can be accounted for in terms of changes occurring at the level of the lateral geniculate nucleus.
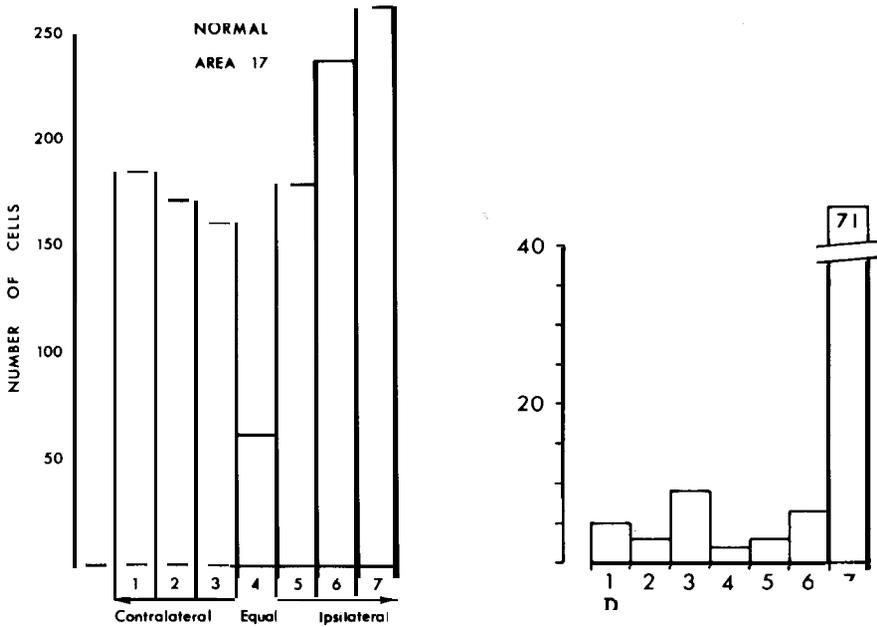
Fig. 1. Ocular dominance histograms in normal and monocularly deprived rhesus macaque monkeys.

Left histogram: 1256 cells recorded from area 17 in normal adult or juvenile rhesus monkeys. [13]

Right histogram: obtained from a monkey in which the right eye was closed at 2 weeks for 18 months.[15] It shows the relative eye preference of 100 cells recorded from the left hemisphere. The letter D indicates the side of the histogram corresponding to dominance by the deprived eye.

Cells in layer IVC are excluded in this figure and in histograms of all other figures. Cells in group 1 are driven exclusively from the contralateral eye, those in group 7 from the ipsilateral eye, group 4 cells are equally influenced, and the remaining group are intermediate.

Although the cells lying in the geniculate layers that receive input from the deprived eye are smaller than those in the non-deprived layers (Fig. 2) they are present in normal numbers, respond briskly to stimulation of the deprived eye and have normal receptive fields. Since geniculate cells are functionally normal and the cortical cells are altered in their properties there must be some change in the effectiveness of the geniculocortical connections. We were interested in investigating whether there were any structural changes associated with this abnormality.

The first aspect of cortical organization to be examined is the pattern of input of the geniculate afferents to the cortex. This can be done using the autoradio-graphic technique for tracing neuronal connections, transynaptically from the eye[18, 20] or by a fiber stain [19] (see also lecture of David Hubel). When in the normal monkey the input from the lateral geniculate nucleus reaches layer IV of the cortex, the information from the two eyes is still segregated. The input from each eye is distributed into a series of branching and anastomosing bands, which are about 0.5 millimeter wide, and alternate with similar bands serving the other eye (Fig. 3A). This pattern of innervation forms the anatomical basis for ocular dominance columns. Cells in the superficial and deep layers, while

Fig. 2. Coronal section through the right lateral geniculate nucleus of the monkey with right eye closed at 2 weeks for 18 months (Fig. 1, right). Note the atrophy in the layers receiving input from the deprived eye (indicated by arrows). Stained with cresyl violet; frozen section. [13]

tending to be more binocular than cells in layer IV, still are more strongly influenced by the eye that provides input to the column in which they reside. The relative influence of the two eyes is shown by making tangential electrode penetrations through different cortical layers. Such penetrations in the normal monkey show regular changes in eye preference as expected from the columnar arrangements (Fig. 3A; Fig. 4, top).

In an animal that has undergone monocular deprivation, the geniculate terminals with input from the non-deprived eye take over much of the space that would normally have been occupied by terminals from the deprived eye (Fig. 3B). [13,15] The deprived eye input has shrunken down to occupy the small strips lying between the terminals of the non-deprived eye input. Tangential electrode penetrations through cortical layers reveal long expanses of cells driven by the non-deprived eye interrupted by small patches of cells that are either unresponsive or driven by the deprived eye (Fig. 4, middle). As will be
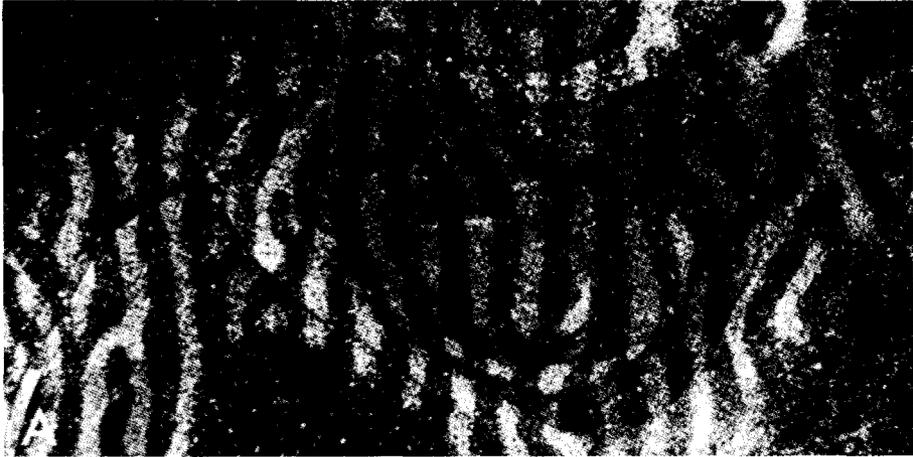
Fig. 3. Dark field autoradiographs of monkey striate cortex following injection of ^{3}H-proline in the vitreous of one eye 2 weeks before.

   A: Normal monkey, a montage of a series of tangential sections through layer IVC. The light stripes, representing the labelled eye columns, are separated by gaps of the same width representing the other eye. B: Monocularly deprived monkey, again a montage from a series of tangential sections through layer IVC. Same monkey as in Fig. 1, right, and Fig. 2, which had the right eye closed at 2 weeks for 18 months. The input from the normal eye is in form of expanded bands which in places coalesce, obliterating the narrow gaps which represent the columns connected to the closed eye.
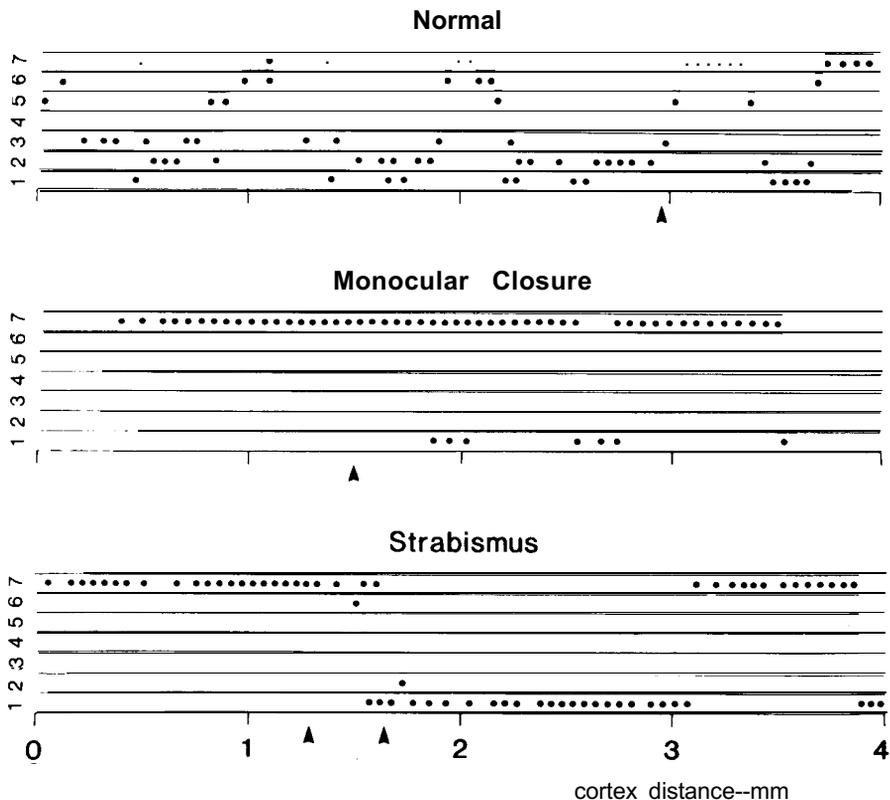
Fig. 4. Eye preference of cells recorded in oblique penetrations through the cortex in a normal monkey, a monocularly deprived monkey, and a monkey raised with strabismus. Ocular domi-nance categories (l-7) are shown relative to the distance the electrode penetrated through the cortex.

Top: Penetration in a normal monkey which shows the sinusoidal shift in eye preference with distance. The arrowhead indicates that the electrode entered layer IVC, in which cells are monocular, and there are abrupt shifts of dominance from one eye to the other.

Middle: Oblique penetration in a monkey raised with monocular closure (same monkey as in Figs. I-3). Note that outside layer IV all cells are driven only by normal eye (7), and in layer IVC (see arrow) there are only short stretches of cells with input from the deprived eye. The observed overlap of input from left and right eye is not present in the normal monkey.

Bottom: A monkey with a 10° convergent squint produced by sectioning of the lateral rectus at three weeks. (Same animal as in Fig. 11, left histogram). The illustration shows the result of oblique penetration through the striate cortex made when the animal was 3½ years old. Even outside of layer IV cells were monocular, with equal stretches of cortex dominated by either eye.

shown later in this paper, this expansion of the input from the non-deprived eye occurs at the level of single geniculate afferents. Cells in the deprived layers of the geniculate are smaller than normal. One reason for this is that their shrunken cortical arbors may require a smaller soma to maintain them, as originally proposed by Guillery and Stelzner (1970). [26]

Morphological examination of the lateral geniculate nucleus in these animals showed that there is a good relationship (r = 0.91) between the relative size of normal and deprived cells and the relative size of normal and deprived

ocular dominance columns in layer IVC. [15] Thus, measuring geniculate cell sizes is yet another means of evaluating the effects of monocular closure.

From the histogram shown in Fig. 1 one cannot tell whether many cells have changed allegiance from the deprived to the non-deprived eye or have simply become unresponsive. The autoradiographic labelling of the afferents in layer IV (Fig. 3B) shows that a greater proportion of the cells in layer IV receive direct input from the non-deprived eye. The consequence of this change is that cells at later stages have shifted their allegience from the deprived to the non-deprived eye, rather than becoming unresponsive. This conclusion is supported by the physiological findings that the large majority of cells in superficial and deep layers respond only to the stimulation of the normal eye (Fig. 4, middle).

THE CRITICAL PERIOD

Having observed these dramatic effects of monocular suture early in an animal's life, we wanted to determine if there was a period over which the cortex retained its plasticity.

Our experiments in adult cats and monkey [6,15] showed that long periods of monocular lid suture did not result in the sort of changes in the visual cortex described above. Instead, we found that there is a definite period of time, early in life, during which the visual system shows this lability. We termed this the "critical period." The permanent visual deficits observed in children with congenital cataracts are therefore most likely a result of changes in the visual cortex that occurred during the critical period. Adult humans suffering from cataracts for many years will have normal vision when the cataracts have been removed presumably because they are well past their critical period at the onset of the disease.

The critical period in the monkey was estimated by closing one eye at different ages and keeping it closed for several months or longer. [15] The deprivation effect was gauged by the relative influence of the two eyes on single cortical cells (ocular dominance distribution), by the distribution of the input from the two eyes in layer IV (using the autoradiographic technique shown in Fig. 3), and by comparing the cell sizes in deprived and non-deprived layers of the LGN. The physiological results in monkeys with one eye closed at 2 weeks, 10 weeks, 1 year of age, and in the adult are illustrated in terms of ocular dominance histograms in Fig. 5. The earliest closure produced the most severe shift of preference toward the normal eye. The same degree of shift could be seen up to an age of 6 weeks. At that age the animal's susceptibility to monocular deprivation began to decline, but as is shown in the figure, it was still pronounced at 10 weeks and was detectable at one year. As indicated above, there were no cortical changes when the closure was done in the adult.

The changes occurring in the geniculo-cortical innervation were in general agreement with the physiology, though the time course was somewhat different (Fig. 6). Animals with a closure at 2 and 5½ weeks showed the expected expansion of the non-deprived geniculate terminals; closure at 10 weeks showed a more moderate expansion, and at one year the pattern was indistin-
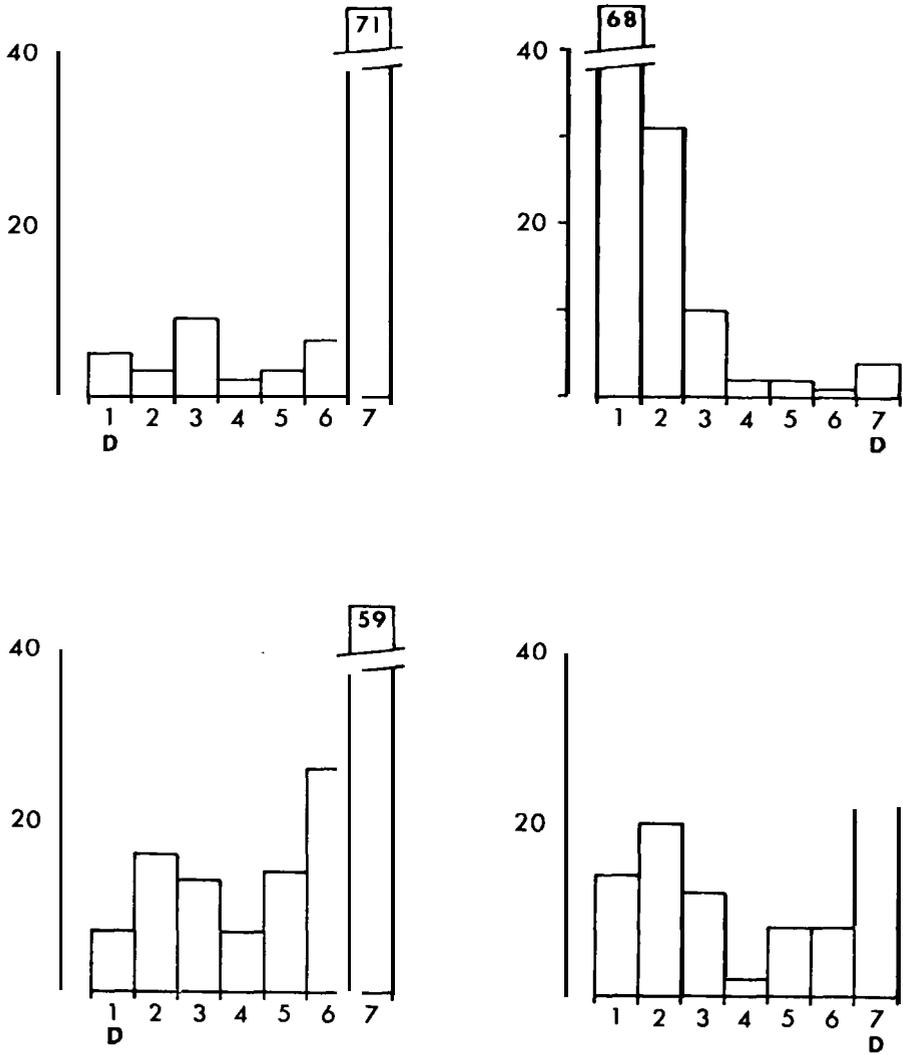
Fig. 5. Ocular dominance histograms of monkeys with one eye occluded by lid suture at different ages and examined after relatively long periods of closure. [15]

Upper left: Same monkey as in Figs.1-4. Right eye closed at 2 weeks for 18 months (cf. Fig.1, right).

Upper right: A monkey with right eye closed at 10 weeks for 4 months. Strong dominance of normal eye but not as pronounced as at earlier closure. Duration of deprivation relatively short, but our experience is that at this age the main changes in eye preference occur within the first few months of closure.

Lower left: A monkey with right eye closed at 1 year for a period of 1 year. A moderate shift in preference toward the non-deprived eye. This was particularly true for cells in layers II and III.

Lower right: Adult monkey (6 years old) with one eye occluded for 1½ years. There was no obvious difference in eye preference from that observed in the normal monkey.

guishable from that in the adult. Geniculate cell sizes in the deprived layers changed in a parallel fashion, showing marked shrinkage at early closures, moderate reduction in closure at 10 weeks and no change when closed at one year. Since in the closure at one year we observed physiological changes in the
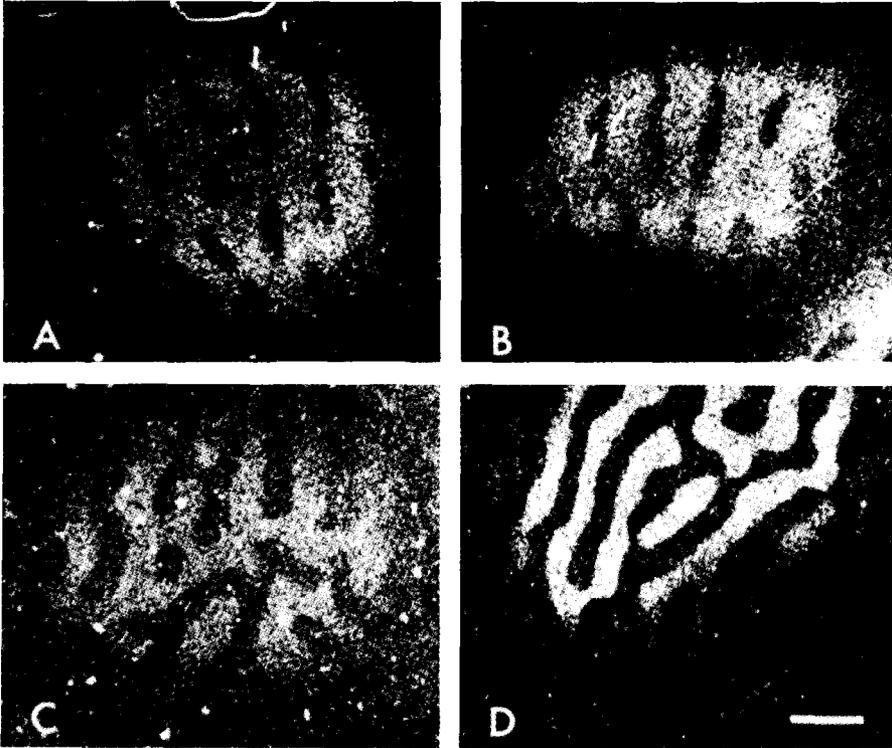
Fig. 6. Autoradiographic labelling patterns from the striate cortex of four monocularly deprived monkeys illustrating the distribution of geniculate terminals in layer IVC after closures at different ages. In all cases the normal (left) eye was injected with ^{3}H-proline thereby labelling the non-deprived geniculate terminals. [15]

A: Right eye closed at 2 weeks for 18 months. Same animal as in Fig. 1 (right), Fig. 4 (middle) and Fig. 5 (upper left).

B: Right eye closed at 5½, weeks for 16 months,

C: Right eye closed at 10 weeks for 4 months. Same animal as in Fig. 5 (upper right).

D: Right eye closed at 14 months for 14 months. The unlabelled bar is 1 mm.

absence of a change in the pattern of geniculate innervation, there must presumably be changes occurring at subsequent levels in the cortical circuit. [13, 14] At any rate, in the adult even this "higher level" of plasticity disappears.

The high degree of susceptibility to deprivation at early ages is also apparent from experiments in which one eye in monkeys was closed for short periods. Before 6 weeks of age, it was sufficient to close an eye for a few days to obtain substantial change in eye preference. The ocular dominance histogram from a monkey with one eye closed for 12 days is shown in Fig. 7 (left). During the subsequent several months a marked change required several weeks of closure, and during the second year any change required months of closure.

From these and similar experiments by us   [13], [15] and others [14,27] we con-clude that the macaque monkey is highly susceptible to monocular deprivation during the first six weeks of life, at which age the sensitivity declines progres-sively, so that at 1½ to 2 years the monkey loses this type of neural plasticity.
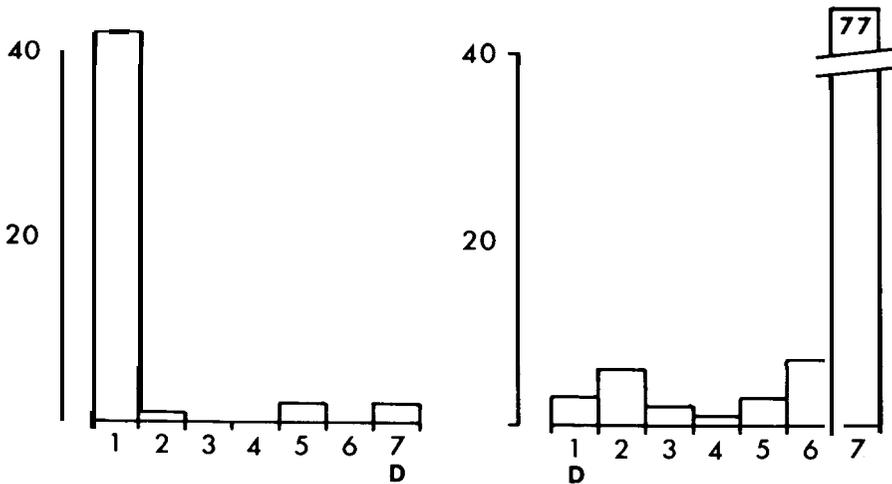
Fig. 7. *Left:* Ocular dominance histogram for 47 neurons recorded in a 20-day-old monkey whose
right eye had been closed since 8 days of age. The physiological picture is similar to that seen after
months of deprivation. [15]

Right: Ocular dominance histogram of 99 cells recorded in a monkey whose right eye was closed
from 21 to 30 days of age. In spite of a subsequent 4 years of binocular vision, most cortical neurons
were still unresponsive to stimulation of the right eye.'"

The length of the critical period varies between species. In cats it is 3 to 4
m o n t h s,[9, 28] and from clinical observations in humans it may extend up to 5 - 10
years, though the susceptibility to deprivation appears to be most pronounced
during the first year and declines with age.   [29, 30, 31]

RECOVERY FROM DEPRIVATION

Monocular closure during the-entire critical period in cats and monkeys leads
to permanent blindness. [32, 33, 34] Presumably there is no recovery of vision
after the eye is opened because the pattern of geniculate innervation and the
eye preference of cortical cells can no longer be modified. During the period of
high susceptibility partial recovery of vision in the deprived eye is possible after
brief periods of monocular closure. [15, 34' 35, 36] This was shown in a monkey
with one eye closed between days 21-30, after which the monkey lived with
both eyes open for a period of 4 years. Initially the animal appeared blind in the
deprived eye but, with time, it slowly regained the use of the eye and the final
acuity was 20/80-100 as compared to 20/40 in the non-deprived eye. The
recordings from the striate cortex showed a marked dominance of the non-
deprived eye (Fig. 4, right). If there was an increase in the number of cells
driven by the once deprived eye, it was not very obvious. There was a marked
narrowing of the deprived columns and a corresponding widening of the non-
deprived ones. Thus, even if there had been some behavioral recovery, these
results demonstrate that a few days of monocular closure had caused clear
physiological and anatomical changes in the striate cortex.
    These results are relevant to observations in children who have been mono-

cularly deprived for short periods of time. When tested later, some children were found to have reduced acuity in the once patched eye and the degree of deficit depended on how young the child was at the time of patching. [38, 39] The experience in children with cataract removal indicates that surgery must be performed very early in the critical period in order to prevent the appearance of any deficit. [40, 41]
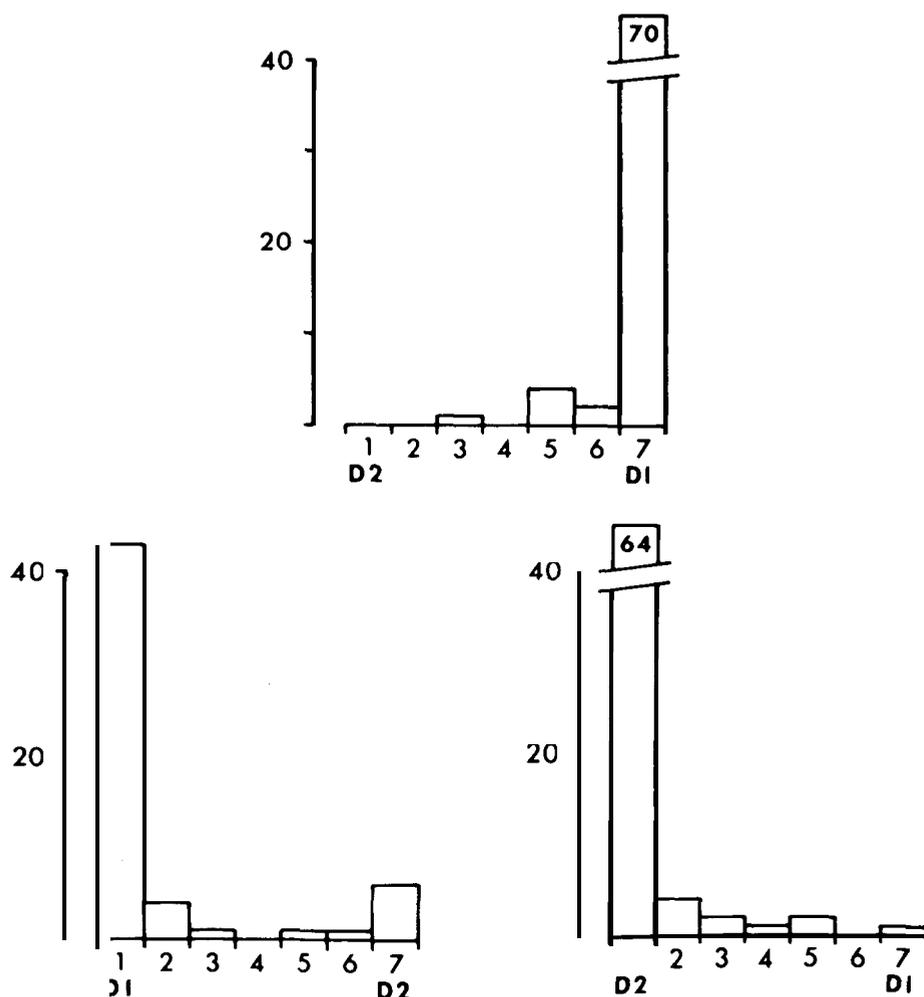

Fig. 8. Ocular dominance histograms of cortical cells recorded in three monkeys in which reversed suture was done at various ages. [15]

Upper histogram: 77 cells recorded from the right striate cortex of a monkey with the right eye (D_1) closed at 2 days for 3 weeks and the left eye (D_2) closed at 3 weeks for about 8 months. Nearly all neurons responded only to the initially deprived right eye (D_1).

Lower left: 56 neurons recorded from the left striate cortex. Right eye (D_1) closed at 3 days for 6 weeks; left eye (D_2) closed at 6 weeks for 4½ months. Again nearly all neurons were driven exclusively by the initially deprived right eye (D_1).

Lower right: 74 neurons recorded from the left striate cortex. Right eye (D_1) was closed at 7 days for 1 year; left eye (D_2) was closed at 1 year for 2½ years. In this case there was no effect of the reversal; nearly all the calls responded only to the initially open eye.

A procedure commonly used in children with strabismic amblyopia is to place a patch over the good eye to improve vision in a weak eye. In monocularly deprived animals it was possible to open the sutured eye and close the normal eye, here termed "reverse suture". Both in the cat and monkey, reverse suture led to a complete switch in eye preference if it was done within the early part of the critical period. [15, 27, 28, 37] The geniculate innervation of layer IVC also reversed so that the shrunken regions controlled by the initially closed eye expanded at the expense of the other eye, and consequently the cortical cells switched eye preference in favor of the eye closed first. [15, 37, 42] An example is shown in Figure 8 (top) in which the eye reversal was done at 3 weeks, and the recordings done 8 months later. The ocular dominance histo-
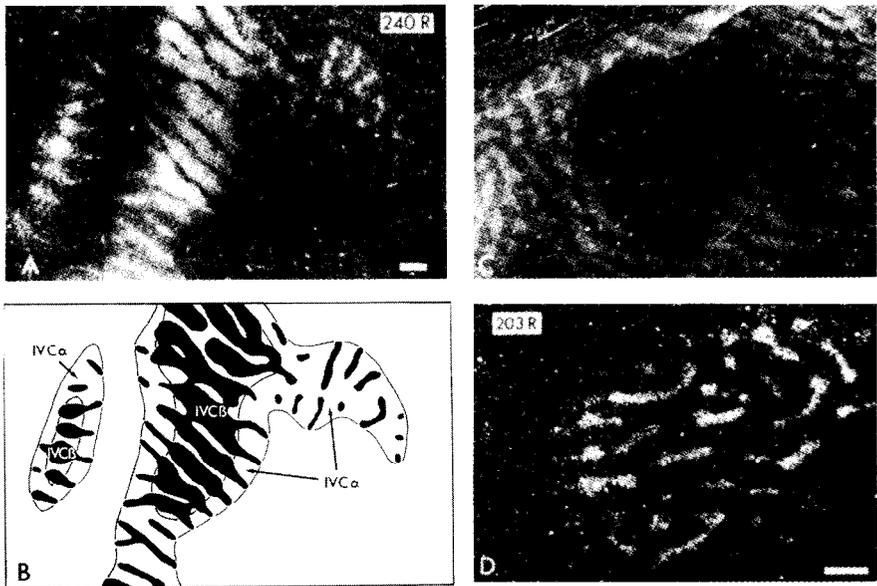

Fig. 9. Effect of reversed suture at various ages on the labelling pattern of geniculate terminals in layer IVC.

A: Same monkey as in the upper part of Fig. 8, in which reversed suture was done at 3 weeks of age. The initially deprived (right) eye was injected with ^{3}H-proline. A single tangential section. In the central region the labelled bands are expanded. In the surrounding belt the bands are contracted. These two regions correspond to the ß and a sublaminae of layer IVC. Unlabelled bar is 1 mm.

B: Key to A, showing the distribution of label (in black) and the boundaries of the sublaminae IVCa and IVCß, traced from an adjacent section stained with cresyl violet. Note that the thin labelled bands in IVCα run into the centers of the enlarged bands in IVCß, meaning that the two sets of bands, though of very different width, are still in register with each other just as they are in normal animals.

C: The autoradiographic montage of the labelling pattern in monkey with reversed suture at 6 weeks (cf. lower left, Fig. 8). The initially deprived right eye was injected. The labelled bands are of about normal width indicating a recovery from the effects of the early deprivation, but not a complete reversal. Most of the montage shows layer IVCß. In layer IVCα the labelled columns remained shrunken (not illustrated).

D: Autoradiographic montage from the monkey with reverse suture at 1 year of age (Fig. 8, lower right). The labelled columns (for the initially deprived right eye) remain shrunken, indicating that the late reversal did not permit any anatomical recovery. Scalemarker = 1 mm.

gram shows that the initially closed eye, which at the time of eye reversal would have influenced very few cortical cells, now became strongly dominant. The autoradiography (Fig. 9A) shows a marked expansion in layer IVCß of the initially deprived geniculate terminals. When reversal was done at 6 weeks the physiology indicated a complete reversal, with a strong dominance of the initially deprived eye (Fig. 8, lower left). Such a marked shift was not reflected in the innervation of layer IV, in which the initially deprived eye had succeeded only in regaining its normal territory (Fig. 9C). This indicates that a significant part of the changes were occurring at the level of intrinsic cortical connections. Finally, reversing at one eye failed to produce any restoration of the function of the initially deprived eye (Fig. 8, lower right; Fig. 9D). Though it is possible to cause changes by monocular deprivation at one eye (Fig. 5, lower left), it appears to be more difficult to repair connections that have already been changed once.

   Looking more closely at the autoradiography of the geniculate input to layer IVC in the monkey with the reversal at 3 weeks (Fig. 9A and B), one sees a surprising result. The initially deprived eye took over much of the area of innervation of the lower part of layer IVC (IVCß), but failed to reverse the dominance of the other eye in the upper part of layer IVC $(IVC\alpha)$. Apparently, the eye preference of the majority of cortical cells is determined primarily by the cells in IVCß (Figs. 8 top, 9A and B). Layer IVCß is innervated by cells in the dorsal part of the lateral geniculate nucleus (parvocellular layers) and $IVC\alpha$ by cells in the ventral part of the same nucleus (magnocellular layers). The result of the eye reversal experiment indicates that the critical period is different for the two cell types. Whereas the critical period is over for the magnocellular input at 3 weeks, the parvocellular input apparently begins to lose its ability to expand at 6 weeks (Fig. 9C), a time when intracortical connections still show considerable plasticity. This suggests that each functional unit has a unique program of development throughout the brain.

MECHANISM: DISUSE VERSUS COMPETITION

These experiments demonstrate that when a binocular cortical cell is not stimulated by a given eye, then the input from that eye drops out. Other forms of visual deprivation have shed some light on the mechanism of the effect of monocular deprivation. For example, if disuse were an important factor, one might expect that with both eyes closed, cortical cells would not be driven by either eye. Experiments in cats and monkeys raised under conditions of binocular deprivation showed, however, that cells were readily driven by the two e y e s .[28, 43, 44] T he cortex in the monkey was nonetheless altered in a very substantial way, in that very few cells were binocularly responsive.   [44] This is illustrated in Fig. 10, in which a monkey had both eyes sutured from birth to 4 weeks of age. Except for the obvious lack of binocular cells, the cortex seemed quite normal. The cells were briskly responsive, showed a high degree of orientation selectivity, and had regular sequences of shifts in orientation preference. From tangential electrode penetrations we were also able to see a clear
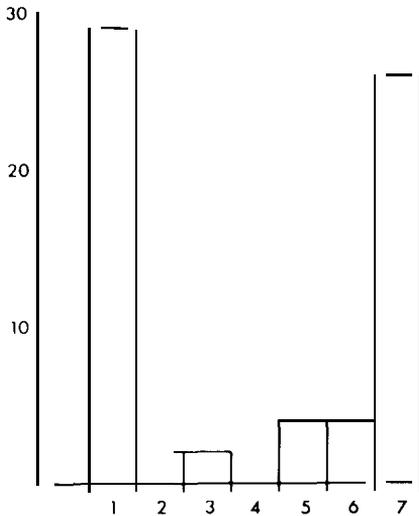
Fig. 10. Ocular dominance histogram of a monkey with binocular lid suture from birth to 30 days
of age. Note the low number of binocular cell. [44]

segregation of the cells into unusually distinct ocular dominance columns, even
outside of layer IV. When monkeys are kept in the binocularly deprived
condition for many months a considerable fraction of the cells are unresponsive
or respond only sluggishly, and often show lack of orientation preference.
Binocular closures in kittens had a similar effect except that neither short nor
long term deprivation led to an obvious loss of binocular cells. [28, 43]

Evidence for competitive mechanisms has also been found by measurements
of geniculate cell sizes in an ingenious set of experiments. [26, 45, 46] First it was
demonstrated in monocularly occluded kittens that deprived cells in the mono-
cular segment of the nucleus were of normal size, whereas those in the binocu-
lar segment showed marked shrinkage. [26] Next Guillery produced a monocular
region in the zone of binocular overlap by making a local retinal lesion in the
normal eye of monocularly occluded kittens. [45] Again the deprived geniculate
cells with no competitive input from the other eye were of normal size, and
those outside the topographical area corresponding to the retinal lesion showed
the usual shrinkage. Finally, it could be demonstrated that binocular closure in
kittens apparently did not lead to a reduction in geniculate cell size [46] a s
originally reported by us. [43] These experiments lend strong support to the
hypothesis that competitive mechanisms rather than disuse are prime factors in
producing the changes observed under conditions of monocular deprivation.

Because many cortical cells are binocular from birth, the loss in the monkey
of binocular cells at early times after closure suggests that in order for cortical
cells to sustain a binocular input the two eyes must work together. Another
situation that interrupts coordinated activity from the two eyes is strabismus. [47]
One way of producing experimental strabismus is to section an extraocular
muscle. Sectioning the lateral rectus causes the eye to deviate inward (conver-
gent strabismus), whereas sectioning the medial rectus produces an outward

deviation of the eye (divergent strabismus). After surgery the sectioned muscle usually reattaches behind the original site, so that except for the misalignment, normal eye movements are restored. In four monkeys with convergent strabismus the operation was performed between 3-5 weeks. [48] When the animals were examined after a year or more, three of them had normal acuity in both eyes but lacked the ability to fuse the images in the two eyes. The striate cortex of these animals had normal single unit activity, but there was a striking absence of binocular cells (Fig. 11, left). Tangential penetrations showed that the monocular cells were grouped in the usual regular columnar pattern (Fig. 4, bottom), suggesting that binocular cells had lost the input from the non-dominant eye. The fourth monkey had low acuity in one eye and fewer cortical cells were driven from that eye than from the normal eye (Fig. 11, right). When in live additional monkeys a strabismus was produced at later times during the critical period, there was an increase in the proportion of binocularly driven cells. From these results and experiments in cats and monkeys reported ear lier[49, 50, 51] it seems that the period during which the cortex can be influenced by the artificially induced strabismus is comparable in duration and sensitivity to that observed with monocular deprivation.
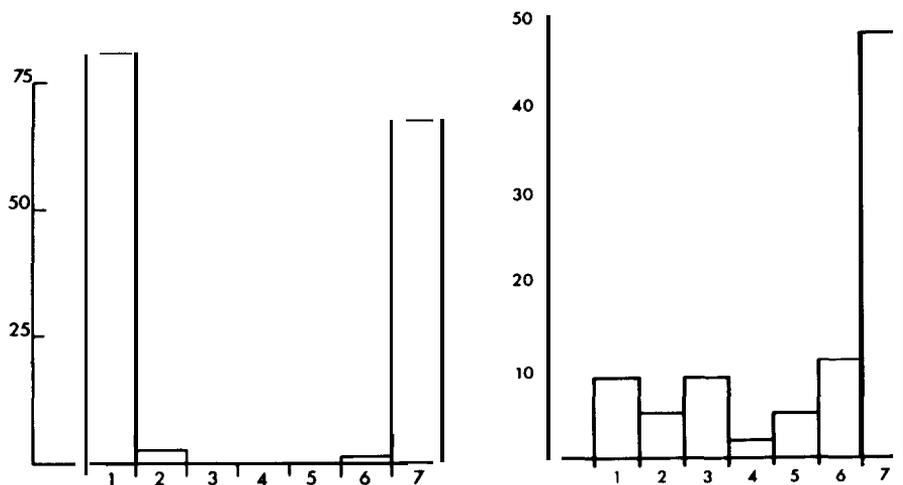

Fig. 11. Ocular dominance histograms of cells recorded in the striate cortex of two strabismic rhesus monkeys. [48]

Left: Histogram shows the eye preference of cells recorded in a 3 year old monkey in which the lateral rectus of the right eye was sectioned at 3 weeks of age. There is a nearly complete absence of binocular cells; the cells are driven exclusively either by the right or the left eye. As shown in Fig. 4 (lower) cells are clustered in a columnar fashion. The monkey had a 10° convergent strabismus, normal acuity in both eyes, but could not fuse images presented separately to the two eyes.

Right: A monkey with lateral rectus muscle of the right eye sectioned at 3 weeks. The animal had a convergent strabismus. Behavioral testing showed normal acuity in the left eye (20/30) and lower acuity in right eye (20/60 to 20/120). There was no difference in refraction between the two eyes. The histogram shows that the amblyopic eye influenced fewer neurons in the superficial and deep layers of the striate cortex. The ocular dominance columns in layer IVC had normal appearance when examined in tangential sections stained with a reduced silver method (Liesegang). [19]

The binocular deprivation and strabismus experiments support the notion that competition, rather than disuse, is the main cause of the observed changes.[43] The right circumstances must exist, however, for the competition to occur, since cells in the normal monkey tend to be dominated by one eye or the other," and the dominant eye does not take over the cell completely. The difference between normal and deprived animals is that under normal conditions a cell receives input synchronously from the two eyes, whereas in monocularly deprived, strabismic, or binocularly deprived animals the two eyes do not act together. The maintenance of a given input may depend on the rate of firing of the postsynaptic cell while that input is active[3] so that in normal animals the non-dominant input is maintained by the activity of the dominant input. Carefully designed experiments by Singer et al[52] and Wilson et a1[53] have provided support for the notion that it is crucial to activate the postsynaptic cell in order to change ocular dominance (for a more general discussion of synapse formation and stabilization see references 54 and 55).

In addition to providing insight into the mechanisms of development and plasticity in the visual cortex, the strabismus experiments may be of direct clinical relevance. A common situation in children with strabismus is that they have good vision in both eyes, but cannot fuse the images in the two eyes. These children often use the two eyes alternately, fixating and attending first with one eye and then with the other. The lack of binocular cells in strabismic animals is perhaps the physiological basis of this condition.[47,12] Another common consequence of strabismus in children is a loss of acuity in one eye (strabismic amblyopia). The physiological mechanism of this condition is less well understood, even if our experiments (Fig. 11, right) and those of others[12,56] indicate that one eye has been weakened in its ability to drive cortical cells, as is seen in monocular deprivation.

As mentioned above, late monocular deprivation in the monkey (see Fig. 5, lower left) and reversal experiments (Fig. 8, lower left, and Fig. 9C) caused alterations in the cortical circuit at stages subsequent to the input from the lateral geniculate nucleus. Another series of experiments illustrated this point quite dramatically. The approach is a variation of the original experiments by Hirsch and Spinelli[57] and by Blakemore and Cooper[58] in which kittens were raised viewing only stripes of one orientation. In our experiments we allowed a monkey to see vertical stripes through one eye only.[59] The other eye was deprived by lid suture. This effectively produced a different condition of deprivation for different populations of cortical cells: those with vertical orientation preference were monocularly deprived, and those with horizontal orientation preference were binocularly deprived. We recorded from the striate cortex after 57 hours of exposure (between days 12-54 after birth) and found normal levels of activity and cells of all orientations with their usual regular columnar arrangement.[17] There was an overall dominance of the open eye, but when we produced separate ocular dominance histograms for vertically and horizontally oriented cells (Fig. 12), it became clear that horizontally oriented cells tended to be driven monocularly by either eye (a picture typical of binocular deprivation), and vertically oriented cells tended to be driven mono-

cularly by the exposed eye only (a picture typical of monocular deprivation). Thus, these findings again demonstrate that in addition to influencing the thalamocortical input, deprivation can alter the connections in the cortex without causing changes in that input. This question has also been addressed in the kitten by somewhat different approaches but with essentially the same results.[60, 61]

In looking at the effects of various forms of deprivation one gets certain insights into the processes that govern the balance between different inputs, enabling the visual cortex to integrate information in the appropriate manner. We have learned that competition and synchronization of inputs are important factors in forming and maintaining this balance. If these processes are disturbed early in life, the system can be permanently altered.

NORMAL DEVELOPMENT

We cannot properly evaluate the experiments on visual deprivation without having detailed knowledge about the normal development of the visual system. To assess the relative importance of the genetic program and the visual environment, it is necessary to evaluate the capabilities of the visual cortex at birth. The monkey is visually alert at or very soon after birth and cells in the
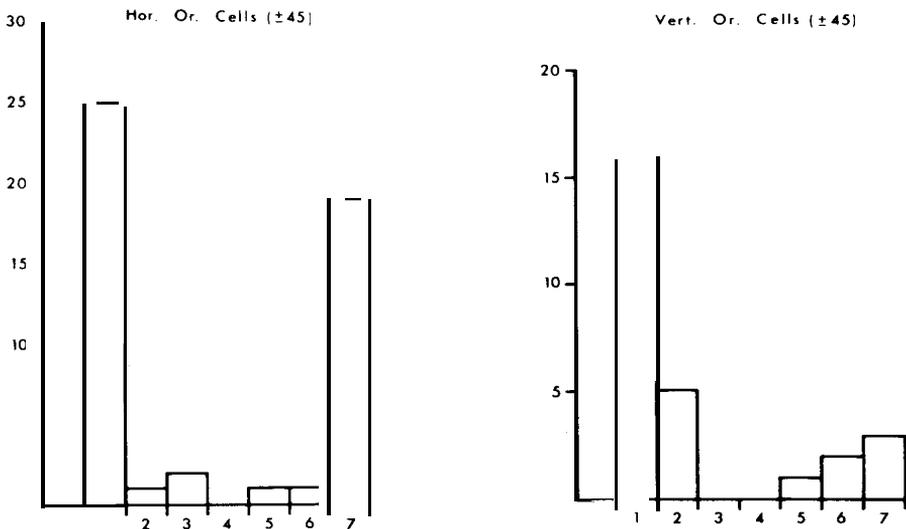

Fig. 12. Ocular dominance histograms of cells recorded from a monkey with the right eye closed at 12 days of age, then dept in the dark except for 57 hours of self-exposure to vertical stripes during the subsequent 42 days.

Left histogram: 48 cells recorded in the right striate cortex with preferred orientation within ± 45° of the horizontal axis. There were few binocular cells and a good number of monocular cells responding to stimulation of either the left or the right eye. Similar distribution of eye preference to that seen in binocularly deprived animals (cf. Fig. 10).

Right histogram: 27 cells with preferred orientation within ± 45° of the vertical axis. Majority of the recorded cells responded to the open eye producing a histogram similar to that seen after monocular deprivation. [59]

visual cortex show orientation preference and binocularity, as in the adult monkey. This was shown by single cell recordings in neonatal monkeys with no experience of contours or forms. [44]

Compared to the monkey, the kitten is far less well developed at birth; the eyes do not open until the second week and kittens tend to spend their first three weeks mainly eating and sleeping. In the visual cortex cells tend to give weak or erratic responses during the early postnatal period and come to respond like adult cells at about 3-4 weeks of age. [9, 28, 62] During the same time period cortical cells differentiate and active synapse formation takes place. [63, 64] Whether cells in the cat visual cortex develop normally without visual experience, as was originally reported for binocularly sutured kittens,* was questioned at first [65] but subsequently confirmed in several studies. [62, 66, 67, 68] Whether in the kitten all cortical cells can develop fully through innate mechanisms is not entirely clear, since animals raised in the dark or with binocular lid closures seem to have a certain fraction of unresponsive or unoriented cortical cells. [62, 66, 68]

The newborn animal does differ from the adult in one significant respect, relating to the segregation of the afferents from the two eyes in layer IVC. In the newborn monkey we were able to show by eye injection of ^{3}H-proline that the inputs from the two eyes are strongly overlapping with only a mild fluctuation in eye dominance in a bandlike pattern. [13] Sokoloff and his colleagues [69] confirmed this observation using the 2-deoxyglucose method. In the monkey foetus Rakic showed that initially the left and right-eye afferents overlap completely, and not until a few days before birth do they begin to sort out into ocular dominance columns. [70] We followed this process of segregation postnatally; it was completed by 4-6 weeks of age (Fig. 13). [13] Recordings also indicated an initial overlap, followed by separation of the inputs from the two eyes in layer IVC and the time course of the events *were* similar. The process of segregation did not require visual experience, since it also occurred in an animal raised in the dark. [15] In kittens ocular dominance columns are formed much as they are in monkeys, showing a sequence of initial overlap and segregation during the first few months of life," even though in this species visual experience appears necessary for their normal development. [72]

In the kitten it has been possible to examine the segregation of ocular dominance columns at a single cell level. In the early postnatal period, a single geniculate afferent gives off numerous branches innervating without interruption an area covering several future ocular dominance columns without interruption (Fig. 14, top). [73] As the axon matures, there appears to be a selective loss of branches, so that ultimately it innervates ocular dominance columns serving one eye and leaves gaps for the columns serving the opposite eye (Fig. 14, middle). [74, 76] In a cat monocularly deprived during its critical period, a geniculocortical afferent with input from the normal eye is shown in the bottom of Fig. 14. [77] It appears to have innervated an area that normally would have been occupied by the other eye.

Both the autoradiography (Fig. 3) and the single cell reconstructions (Fig. 14) suggest a mechanism for the expansion and contraction of ocular domin-
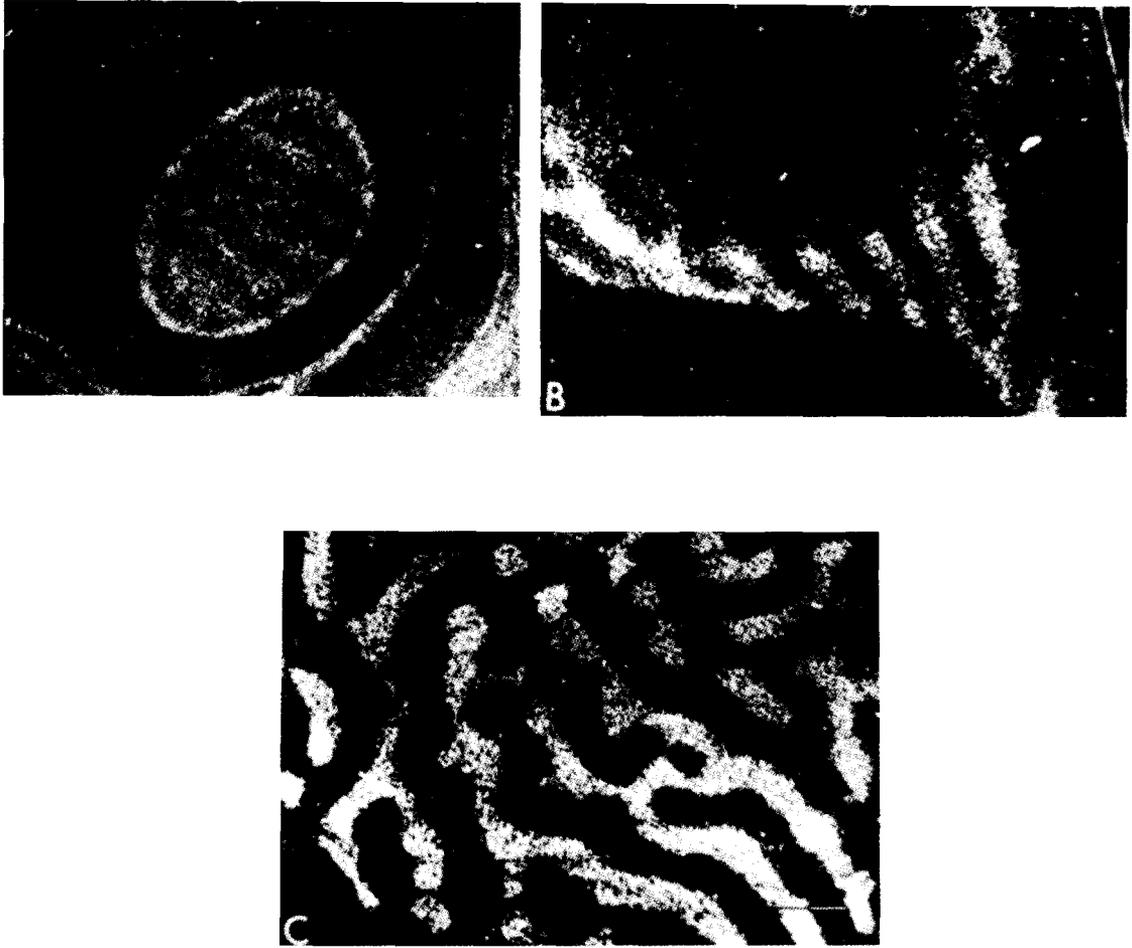
Fig. 13. Darkfield autoradiographs of geniculate afferent terminals in the striate cortex of normal neonatal monkeys in which the right eye had been injected with a radioactive tracer 1-2 weeks earlier. [15]

A: A normal 6-day-old monkey; single section from the left hemisphere that graces IVC tangentially in the central oval region. Silver grains are distributed continuously over layer IVC, but there are bands of alternating higher and lower grain density, indicating that afferents for the two eyes are in the process of columnar segregation.

B: A normal 3-week-old monkey; a single section through layer IVC of the left hemisphere which shows a clear columnar pattern but with a slight blurring of the margin of labelled bands, suggesting a modest intermixing of left and right eye afferents at the borders of ocular dominance columns.

C: A 6-week-old normal monkey; autoradiographic montage of the geniculate labelling pattern in layer IVC of the right striate cortex. The ocular dominance columns appear as sharply defined as in the adult monkey. The unlabelled bar is 1 mm. Adapted from Reference 15.
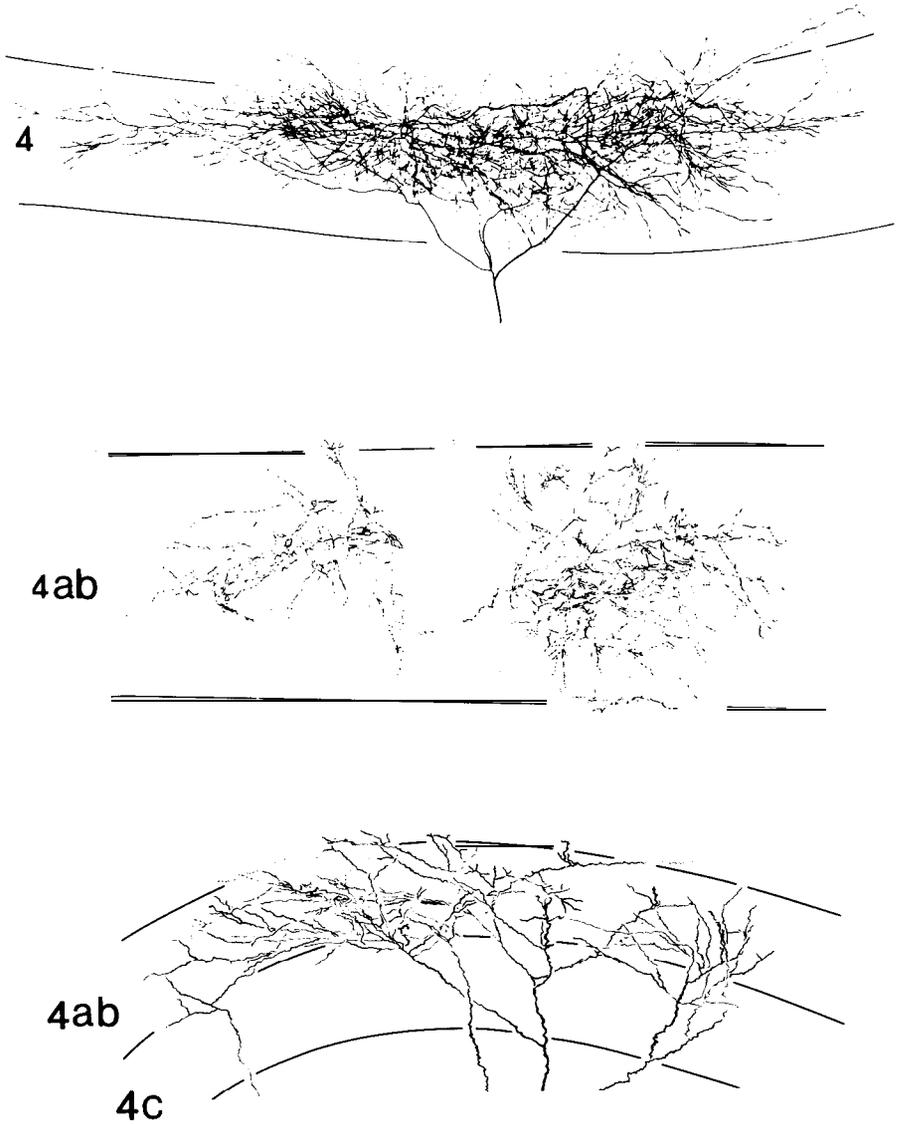
Fig. 14. Patterns of arborization of single geniculate axons in layer 4 of cat visual cortex.
Upper: A l7-day-old kitten; the arborization of a single afferent is shown at an age prior to the
columnar segregation. [71] The axon, impregnated in its entirety with the Rapid Golgi method,
arborizes profusely and uniformly over a disc-shaped area that is more than 2 mm in diameter. The
use of this illustration is gratefully acknowledged (LeVay, S. and Stryker, M.P.). [73]
Middle: Normal adult cat; off-center geniculate afferent (Y-type) [75] injected intra-axonally with
horse radish peroxidase (HRP) in the striate cortex. The arborization is entirely within layer 4 ab
and forms two patches separated by a terminal-free gap. Presumably this pattern corresponds to
the segregation of the input from the two eyes in a columnar fashion. [76]
Lower: Monocularly deprived cat (2 weeks - more than I year); a non-deprived Y-type afferent
with an on-center receptive field injected intra-axonally with HRP. The arborization is primarily
within layer 4 ab but does not have the normal patchy distribution of terminals. The absence of a
terminal free region indicates that non-deprived geniculate branches are present in the territory
that normally belongs only to the other eye."

ance columns in monocular closure. The terminals with input from the normal eye continue to occupy the territory which normally they would have relinquished, while the deprived terminals are trimmed to an abnormal extent. Another mechanism appears to operate at slightly later stages: when the ocular dominance columns are fully segregated (at six weeks of age in the monkey), monocular closure still causes an expansion and a contraction of the columns similar to that seen after earlier closure (Fig. 6B). This argues for a mechanism of sprouting by one axon into the territory originally occupied exclusively by the deprived eye. Perhaps sprouting occurs from the axon branches that traverse the ocular dominance columns for the other eye (Fig. 14, middle). Reverse suture experiments also indicate that both trimming and sprouting are involved in plastic changes of the geniculocortical pathway (Figs. 9A, B, C). We know little of the biochemical mechanisms underlying these changes, except for the intriguing observation of the possible role of norepinephrine in neural plasticity.[78] Since the critical period seems to vary in onset and duration between different brain regions and even between layers of an individual cortical area (cf. IVCa and IVCß in monkey striate cortex, [15] Fig. 9A and B) the control of plasticity appears to be specific and localized, not a phenomenon controlled by diffuse processes.

CONCLUSIONS

Innate mechanisms endow the visual system with highly specific connections, but visual experience early in life is necessary for their maintenance and full development. Deprivation experiments demonstrate that neural connections can be modulated by environmental influences during a critical period of postnatal development. We have studied this process in detail in one set of functional properties of the nervous system, but it may well be that other aspects of brain function, such as language, complex perceptual tasks, learning, memory and personality, have different programs of development. Such sensitivity of the nervous system to the effects of experience may represent the fundamental mechanism by which the organism adapts to its environment during the period of growth and development.

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