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VISUAL NEURAL DEVELOPMENT[1]

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INTRODUCTION

In the middle of the journey of our life,
I came to myself within a dark wood where the straight way was lost.

—Dante, *The Divine Comedy, Inferno* I, 1

This review considers the development of function in the visual system of higher mammals, primarily through electrophysiological studies of neuronal properties in the geniculostriate visual pathway. Although we consider neuroanatomical and behavioral findings where they illuminate processes of functional development, we do not pretend to an even or orderly coverage of these areas. For surveys of material on neural development outside the scope of this review, several excellent sources are available (Jacobson 1978, Lund 1978). We assume a modest familiarity with the functional properties of the normal adult visual system; useful background material for this may be found in several recent reviews (Rodieck 1979, Van Essen 1979, De Valois & De Valois 1980, Lennie 1980).

Rather than execute a necessarily superficial survey of this whole area, we have chosen to direct most of our attention toward two basic questions that have been intensive areas for research and that remain unresolved: *First,* to what degree does normal visual neural development depend on adequate visual stimulation in early life? *Second,* in what way, and within what limits, can the environment act to modify visual neural function?

Though it may not seem wise to attempt to review topics embroiled in active controversy, we feel that these critical issues can be well defined and may benefit from dispassionate examination. Dispassionate does not, we hasten to add, mean unbiased or uncritical, and we apologize in advance to those of our colleagues who may feel that their views or findings are slighted here. But the number and variety of positions that find support in

the literature are such that only the most neutral and pallid of reviews could hope to negotiate them without treading on a few toes.

Species A review such as this could easily become an exercise in comparative physiology, for there seem to be substantial differences among species in the degree and manner in which the environment affects visual development. Since our interest is ultimately directed toward human development, our coverage would ideally concentrate on species similar in visual function to man. The large body of evidence on normal function in the macaque monkey would seem to make it the logical candidate; but there is little developmental literature on the monkey, and so for most important issues we will primarily consider data obtained from cats. While the cat's visual system differs in a number of important respects from the primate's (see Rodieck 1979, Van Essen 1979), it appears that in most ways visual development proceeds in the same manner and according to the same rules in the two species.

METHODOLOGY IN DEVELOPMENTAL STUDIES

> All hope abandon, who enter here.
>
> —Dante, *The Divine Comedy, Inferno* III, 9

Those who study development must contend with a host of problems that do not confront students of the adult visual system. It is often essential (and less often practical) to exercise tight control over many aspects of the rearing of subjects, and the peculiar problems of electrophysiological recording in young animals must be overcome.

Rearing

Virtually every study discussed below rests on assumptions about the conditions under which its subjects were reared. When one compares two animals raised differently, there is implicit the idea that in all respects other than the one being compared, the two animals are the same. But raising animals in abnormal visual environments (e.g. total darkness, special illumination, etc) inevitably results in other abnormalities. It is well known, for example, that animals raised in the dark tend to be at greater risk of infection, tend to gain weight less rapidly than their light-reared peers, and when ultimately removed from darkness, often show significant behavioral abnormalities probably unrelated to their visual deficits.

Even if these factors could be controlled, it is often difficult to be certain that the visual environment desired in a particular experiment was in fact obtained: sutured eyelids can open; the best fitting goggles can be knocked off or askew; mistakes can be made with darkroom doors. The possibility that significant alterations may result from accidents of this sort cannot be ruled out, but has never been effectively addressed.

Electrophysiology

While techniques of electrophysiological recording in adult animals are well understood and reliable, it is not clear that this is true in very young animals, where problems of three different kinds arise.

PHYSIOLOGY It is widely assumed that the conventional situation adopted for CNS recording, in which the animal is paralyzed with a curariform neuromuscular blocking agent, artificially ventilated and lightly anesthetized, does not markedly affect visual unit properties. There is some support for this assumption in adult animals, where at least for levels of the system up to primary visual cortex it seems that unit properties are little different in awake and lightly anesthetized animals (Wurtz 1969, Noda et al 1971, Schiller et al 1976). So far as we are aware, no comparable evidence exists for young animals, and on general physiological grounds it seems likely that these are more susceptible to physiological stress than are adults. Therefore, much of the controversy discussed below concerning visual response properties in neonates is no doubt muddied by uncertainties about the physiological conditions during recording.

RECORDING While recording methods developed for adults may be used in all but the youngest animals, problems arise from several sources. First, neurons are smaller in young animals, and this may alter the well-known sampling bias shown by microelectrodes. Second, since the skull and its sutures are not fully formed in young animals, the entire recording situation is often less stable, which may restrict the amount of data that can be obtained, especially from smaller, more difficult-to-isolate neurons.

VISUAL STIMULATION In young kittens, if not in monkeys, the optical quality of the eye is much worse than in the adult. While recent evidence suggests that this is not an overwhelming problem (see below), it is clear that the highest retinal contrast levels obtainable in young animals are in some cases lower than the levels needed for effective stimulation, even in adult animals.

EXPERIMENTAL DESIGN Developmental experiments present special problems of variability, both within and between animals, that require special attention to certain aspects of experimental design. In studies of the normal visual system, it is usual to consider data from a number of (presumably similar) adult normal animals; it is rare for data from different animals to differ significantly. Developmental studies often involve a number of rearing conditions, and the number of animals per experimental group is often small as a result. While most experiments tend to assume that the degree of interanimal variability is as low in specially reared animals as it is in normals, it is likely that the problems of rearing and recording alluded to above add significantly to the variance.

Suitable procedural controls for this problem include "blind" procedures in which the experimenter is unaware of the animal's history, and both a regular protocol for sampling from electrode penetrations and histological reconstruction at the end of the experiment that is sufficient to accurately localize the sites at which recordings are made. Ideally, comparisons should be made among animals from each of which data samples of identical size and neuroanatomical distribution have been taken. The abnormally weak and variable responses of many visual neurons in specially reared animals make it most desirable that objective methods (preferably involving randomly interleaved multistimulus experiments, e.g. Henry et al 1973) be used to study receptive field properties. This is not always practical, in that the greater reliability of data obtained in this way is paid for in the considerably reduced number of units that can be studied.

A perusal of the literature cited in this review will rapidly show how few studies (our own no less than others') satisfy these prescriptions and proscriptions.

Uses and abuses of statistics Conventional parametric and nonparametric statistical techniques make strong assumptions about sample-independence that are clearly not jusified in dealing with neurophysiological data. An obvious example comes from the orientation and ocular dominance column structure of the visual cortex (Hubel & Wiesel 1977), which makes it probable that neurons recorded near one another have similar properties. To take distributions of these properties and subject them to conventional statistical treatment can as a result be grossly misleading. It is therefore most depressing to see the frequency with which this sort of error is made, and with which strong statements and inferences are based on flawed analyses. While it is not impossible to devise statistical techniques that take account of sample dependence, there has been no widespread serious attempt to apply these to questions of visual development.

NORMAL VISUAL DEVELOPMENT AND EFFECTS OF TOTAL DEPRIVATION

> But so much the more malign and wild does the ground become
> with bad seed and untilled,
> as it has the more of good earthly vigor.
>
> —Dante, *The Divine Comedy, Purgatorio* XXX, 118

If one wishes to study the way in which development can be affected by environmental manipulations, it is essential to have sound data about the course of development in normal environments. A "normal" laboratory visual environment is, of course, in many ways different from a species' natural environment, but it is clearly worthwhile to know how visual function develops in animals raised in the laboratory setting when they are given full daily exposure to light and visual contour stimulation.

The grossly contrasting developmental manipulation is to deprive an animal of all light and pattern stimulation. Two methods are commonly used to produce this deprivation: complete dark-rearing and bilateral eyelid suture. While sporadic reports (discussed below) suggest that there may be some differences between dark-reared and binocularly lid-sutured animals, for most purposes these two rearing conditions appear to yield similar results. Comparing a deprived animal with a normal animal should give some indication of the overall range of effects developmental manipulations may be expected to produce, and allows us to consider the first of our two questions: to what degree does normal visual development depend on adequate stimulation in early life?

Visual Optics

NORMAL DEVELOPMENT Neonatal monkeys and humans possess clear optic media. Although no quantitative measurements of image quality in the infant (or indeed mature) monkey eye are available, ophthalmoscopic examination gives the convincing impression that optical quality changes little after birth in these species. Since both men and monkeys can resolve spatial frequencies in excess of 40 c/deg (Campbell & Green 1965, De Valois et al 1974), it seems likely that optical quality per se does not significantly limit either development or developmental study. Young human infants show some definite abnormalities of accommodation (Braddick et al 1979), are often somewhat hypermetropic (Duke-Elder 1963), and tend to exhibit significant astigmatic refractive errors more often than adults (Mohindra et al 1978, Howland et al 1978); it is not unlikely that young

monkeys show similar effects. But in general the effects of all these optical abnormalities are small compared to the differences in visual performance seen between infant and adult monkeys and humans.

Most of the following discussion centers, however, on the cat; in this species optical quality appears poor near birth and improves dramatically during precisely the period in which most neural developmental activity takes place. The main problem for the young kitten's image-forming apparatus is the persistence of the *tunica vasculosa lentis,* the vascular plexus that supplies the developing lens (Thorn et al 1976, Freeman & Lai 1978). The quality of other optical surfaces of the kitten eye also improves considerably over the first few weeks of life (Freeman & Lai 1978, Freeman et al 1978, Thorn et al 1976). Measurements of retinal image quality in young kittens, however, show that the effect of these imperfections is less than simple ophthalmoscopic inspection would suggest (Bonds & Freeman 1978, Derrington 1979). Even at the age of 16 days, image quality in the young eye is quite respectable; by 6 weeks or so, it is comparable to that seen in adults (Bonds 1974, Robson & Enroth-Cugell 1978). At all ages at which behavioral acuity measurements are possible, measured acuity is lower than that permitted by the optics (Mitchell et al 1976b, Bonds & Freeman 1978). Bonds' measurements suggest that light scatter, which is considerable even in the adult cat eye (Robson & Enroth-Cugell 1978), decreases more slowly than does simple image blur during development. Despite appearances, then, it seems that even in kittens, optical factors are probably not an important constraint on visual development. But it should be noted that the optical deficits in very young kittens are considerable and that it may be difficult to obtain an accurate estimate of refractive state in the young eye; in electrophysiological experiments, then, it is possible that image quality is degraded to a degree that affects the results.

EFFECTS OF DEPRIVATION There is some evidence that eyelid suture (a commonly used deprivation procedure) can radically deform developing kitten and monkey eyes, causing large refractive errors (Wiesel & Raviola 1977, Wilson & Sherman 1977, Gollender et al 1979; but see also von Noorden & Crawford 1978 for a contradictory report). There is, however, no evidence that deprivation produced by other methods results in any significant optical deficits.

Retina

NORMAL DEVELOPMENT The development of functional properties in the retina has until recently been little studied, a curious omission in view of the intense interest in cortical development. Even now, few studies de-

scribe retinal physiological development in any detail, and none of those in species other than cat.

Anatomically, the cat retina is immature at birth (Donovan 1966, Rusoff 1979); even in the central retina, fully adult morphology is apparently not seen until the third week, while the periphery may not be fully mature until some weeks later. Nonetheless, brisk visual responses may be recorded from retinal ganglion cells during the third week of life (Hamasaki & Flynn 1977, Rusoff & Dubin 1977, Hamasaki & Sutija 1979). Quantitatively, the responses of these neurons are less vigorous than those seen in adults, and their receptive fields are distinguished by weak or absent antagonistic surrounds. Until 4 to 5 weeks of age, it is difficult to classify cells as X or Y type by criteria used in adults (Enroth-Cugell & Robson 1966). Hamasaki & Sutija find that most of the cells they can classify in this way in young animals are Y cells, but Rusoff & Dubin's data show no major developmental difference between the two types. Oddly, Daniels et al (1978) report an opposite result for neurons in the lateral geniculate nucleus in kittens of the same ages; X cells there develop earlier than Y cells.

The receptive fields of ganglion cells in young kittens tend to be larger than those in adults. It is difficult to establish to what degree this is due to the weakness of antagonistic surrounds in these neurons, to what degree it is due to light scattered by the optics of the eye, and to what degree receptive field size is actually changing. In addition, the growth of the eye causes changes in the angular subtense of fixed distances on the retina. Rusoff & Dubin (1977) conclude that there is evidence of neural maturation until about 4 weeks of age; thereafter, changes in receptive field size seem to be accounted for by changes in eye size.

EFFECTS OF DEPRIVATION We know of no evidence that visual pattern deprivation procedures produce significant effects on the properties of retinal cells, and there is some evidence that it does not (Sherman & Stone 1973, Kratz et al 1979a). We are unaware of any data on the properties of retinal cells in young monkeys, where the high quality of the optics would make interpretation and measurement much simpler.

Lateral Geniculate Nucleus (LGN)

NORMAL DEVELOPMENT The principal developmental interest in the LGN has until recently been morphological. Wiesel & Hubel (1963a) reported that the responses of geniculate neurons in monocularly and binocularly deprived animals seemed for the most part normal, despite marked failure of cell growth in geniculate laminae connected to the deprived eye.

Much attention has subsequently been paid to this effect, and it will be considered in a later section of this review. Recently, however, more attention has been directed to possible effects of deprivation on LGN physiology and on its normal development.

Daniels et al (1978) studied the development of visual and electrical responsiveness in cat LGN neurons and found similar abnormalities in young animals to those reported above for retinal cells: reduced responsiveness and sensitivity to light, abnormally large receptive fields, and weak or absent antagonistic surrounds. Electrical responses in the young geniculate are grossly abnormal; this is doubtless due in large part to the fact that optic tract myelination is not complete in cats for some weeks after birth (Moore et al 1976). Daniels et al reported that most X cells in the LGN mature before Y cells; as mentioned earlier, this is not in agreement with the order reported in retina. Ikeda & Tremain (1978a) also report early development of geniculate X cells, though they make no specific comment about Y cells being absent. Ikeda & Tremain also reported improvement in the spatial resolution of LGN X cells that continues into the third month of life and that is greater than can be accounted for by the changes in eye size that seem to account for changes in retinal receptive field size. LGN development may significantly lag that of the retina, but since retinal resolution measurements are not available, this conclusion is necessarily tentative.

As in the retina, we are not aware of any data on development of geniculate properties in young monkeys; again, the quality of the optics would greatly ease experimental work in this species by comparison with the cat.

EFFECTS OF DEPRIVATION The most-studied and most controversial effects of visual deprivation in the LGN are those consequent to monocular lid closure; we discuss these below in the context of partial deprivation effects because they seem to be secondary consequences of changes in geniculocortical projection patterns. Dark rearing or bilateral lid suture also appear to affect the LGN, though the available evidence suggests that the effects are subtle compared to those seen in cortex.

Wiesel & Hubel (1965a) reported that bilateral lid closure caused a marked shrinkage of cells in all layers of the cat LGN, but subsequent more extensive measurements by Guillery (1973) showed that this effect is relatively slight. Sherman et al (1972) and Kratz et al (1979b) reported that binocular deprivation reduced the proportion of Y cells recorded from cat LGN, although less dramatically than monocular deprivation did. These and other groups have reported relatively subtle effects of deprivation on the receptive field properties of LGN cells. While most cells appear normal, they may be quantitatively less sensitive than cells in normal LGN. In

addition, Wiesel & Hubel (1963a) and Sherman et al (1972) report a small number of highly abnormal cells, with large, diffuse and insensitive receptive fields.

Visual Cortex

The visual cortex, particularly the striate cortex (area 17, V1), has in the last 10 years or so received more attention in developmental study than any other. While certain effects of deprivation may manifest themselves in the retina and LGN, it seems that it is in the cortex that the most profound and interesting developmental effects are to be seen.

NORMAL DEVELOPMENT Cragg (1972, 1975a) studied the synaptic development of striate cortex, and reported that at the time of natural eye-opening (about 8 days), only a small fraction of the normal complement of synapses could be found. Between that time and the age of about 5 weeks, there is a burst of synaptogenesis; this is followed by a partial loss of synapses until adult levels are reached after the age of 3 months. Quantitatively, this change in synaptic density seems very much greater than the change in physiological properties measured over the same period; it is, however, not obvious how one should compare these two measures of development.

Receptive fields Hubel & Wiesel (1963) studied the properties of a relatively small number of cells in area 17 of young kittens lacking visual experience. While they observed that many cells gave weak and erratic responses and lacked the degree of stimulus specificity seen in adult cortex, they reported that all the fundamental receptive field properties seen in the adult cortex—binocularity, orientation selectivity, and direction selectivity —could be seen in the naive cortex. They also reported recognizable examples of the major cell types seen in adults. This finding was challenged by Barlow & Pettigrew (1971; see also Pettigrew 1974), who claimed that most cells in visually inexperienced kittens lacked stimulus specificity, and that those cells showing stimulus preferences possessed only direction, rather than orientation, selectivity. These views represent two extremes, between which most subsequent claims have fallen. Most other reports on naive kitten cortex confirm Hubel & Wiesel's report that orientation-selective cells can be found (Sherk & Stryker 1976): these seem principally to be of the "simple" type, to be situated in cortical layer IV, and unlike most cells in young kittens, to be monocularly driven (Blakemore & Van Sluyters 1975, Buisseret & Imbert 1976, Fregnac & Imbert 1978, Derrington 1978, Bonds 1979). Some reports (e.g. Fregnac & Imbert 1978, Leventhal & Hirsch 1977) also suggest the intriguing possibility that these cells are

preferentially sensitive to horizontal or vertical orientations. Most of these authors agree, however, that in very young animals many cells lack stimulus specificity, and a sizable minority of isolated neurons cannot be activated by visual stimuli.

Derrington (1978) reported that the spatial resolution and contrast sensitivity of cortical neurons improve markedly between 2 and 6 weeks; his data taken in conjunction with the LGN measurements of Ikeda & Tremain (1978a) suggest that at least the most sensitive cortical neurons at all ages faithfully relay all spatial information passed by the LGN. Until the age of 4 to 5 weeks, however, it is only a small minority of cortical neurons that do this.

Binocularity Since binocular neurons are common in young kittens, it is natural to inquire about the development of the segregated ocular dominance structure present in adult cats (Hubel & Wiesel 1965, Shatz et al 1977, Shatz & Stryker 1978). In adult cats and monkeys, geniculate afferents devoted to the two eyes are segregated into discrete bands in layer IV; in this layer, cells tend to be monocularly driven (Hubel & Wiesel 1968, Shatz & Stryker 1978). While physiological recordings in young monkeys and kittens show evidence of the normal periodic variation in eye dominance seen in adults (Wiesel & Hubel 1974, Blakemore et al 1975a), recent anatomical evidence suggests that the segregation is much less pronounced in young animals and improves markedly in the first postnatal weeks (Rakic 1977, Hubel et al 1977, LeVay et al 1978, LeVay & Stryker 1979). These results, based on transneuronal transport of intraocularly injected amino acid label to the cortex, are weakened by the "leakiness" of axons and axon terminals in young animals—a great deal of "spillover" of the labeled material occurs in the LGN. LeVay et al (1978) attempt to measure and compensate for this spillover, and in so doing come to the conclusion that all the spillover affecting their results occurs in the LGN and none in cortex. They report that their physiological recordings show that layer IV neurons are frequently binocularly activated in young animals, but this result contradicts most other reports (see above). LeVay & Stryker (1979) report that the axonal arborizations of geniculate afferents in cortex lack the "puff" organization thought in adults to reflect ocular dominance bands (Ferster & LeVay 1978), but the presence of axonal branches does not, of course, indicate with certainty the presence of functional synapses.

On balance, the physiological evidence for ocular dominance columns in young animals, combined with the technical difficulties with the anatomical analysis attempted by LeVay and his colleagues, suggest that some segregation by ocular dominance is present in the cortex of young kittens without visual experience. A striking feature of the data presented by LeVay et al

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(1978), although not remarked by the authors, is the very small number of cells dominated by the ipsilateral eye in the neonatal cortex. This is not inconsistent with other reports (e.g. Fregnac & Imbert 1978) and suggests that the phylogenetically more recent ipsilateral pathway might lag slightly in ontogeny.

In a finding consistent with the generally poor quality of receptive fields in young kittens, Pettigrew (1974) shows that the tight selectivity for binocular disparity typical of some cells in adult cortex (Pettigrew et al 1968) is absent in neonates. The development of disparity selectivity over the first few weeks closely matches the development of other receptive field properties (e.g. Derrington 1978, Bonds 1979), and is presumably a secondary consequence of it.

EFFECTS OF DEPRIVATION The critical question that we address in this section concerns the effect of binocular deprivation (BD) on cortical receptive field properties. Inquiry here falls naturally into two parts: what is the effect of long-term visual deprivation, and how does the course of development differ between deprived and normally raised animals?

Long-term deprivation Wiesel & Hubel (1965a) studied cortical unit properties in cats deprived of vision by bilateral lid suture for several months from the time of birth. They produced the most "favorable" report available on cortical function in animals raised in this way. They found that while at least one-quarter of the cells were unresponsive to visual stimuli, and another quarter had poorly defined and unselective receptive fields, most of the remaining neurons had relatively normal receptive field properties. Most subsequent studies have reported considerably more devastating effects of long-term BD than these. Several findings were common to almost all reports: fewer than one-fifth of cells have normal orientation selectivity; a somewhat higher proportion have direction selectivity; at least one-third of the cells are visually unresponsive; most responsive neurons remain binocularly activated, but most of the "normal" cells tend to be monocularly driven (Blakemore & Van Sluyters 1974, 1975; Kratz & Spear 1976; Leventhal & Hirsch 1977; Singer & Tretter 1976; Cynader et al 1976; Fregnac & Imbert 1978; Watkins et al 1978; Bonds 1979). In each report, the experimenters comment on the refractoriness and unreliability of neuronal responses in deprived cortex, and it is clear even though some proportion of cells can be likened qualitatively to those in adults, there are important quantitative effects on the sensitivity and statistical reliability of responses.

Pattern deprivation vs total deprivation It is not clear whether there are important differences between cats raised in total darkness and cats de-

prived by binocular lid suture. Some diffuse light stimulation reaches the retina behind a sutured eyelid (Crawford & Marc 1976): cats can make luminance discriminations with an eye occluded in this way (Loop & Sherman 1977), and responses to visual stimuli can be recorded in the cortex while the lids are still closed (Spear et al 1978). Kratz & Spear (1976) point out that in most cases there is evidence for a loss of binocular interaction following bilateral lid closure, an effect apparently not seen after dark rearing; it must be noted that their results on this point are extreme by comparison with others in the literature. Differences between the two eyes in the pattern of diffuse stimulation they receive might decrease cortical binocularity by the kind of binocular competition mechanism discussed below. Against this view, however, stand the findings of Singer et al (1977) and Wilson et al (1977) that unequal diffuse light stimulation of the two eyes does not alter cortical binocularity.

Leaving binocularity aside, there is some evidence in the literature that dark-rearing may have more deleterious effects on cortical neurons than binocular lid suture: studies involving dark-reared animals usually find a higher proportion of unresponsive cells and a lower proportion of orientation-selective cells than studies involving bilateral eye closure (compare, for example, Pettigrew 1974, and Fregnac & Imbert 1978 with Wiesel & Hubel 1965a and Sherk & Stryker 1976). But in the absence of a well-controlled study of animals raised and recorded in the same laboratory, this is conjecture. The most parsimonious assumption is that most of the effects of BD, however produced, result from the absence of contoured visual patterns on the two retinas.

Time-course of deprivation effects It is clear that BD grossly disrupts cortical function when comparison is made with normally reared adult cats. What is the nature of this effect? Does the cortex of a BD animal end up in a more severely abnormal state than it was near birth, or is there simply a failure of normal development that leaves the cortex "frozen" in its neonatal state? Or, indeed, is there any evidence for passive maturation? The natural way to approach these questions is to compare normally reared and BD animals over a range of ages, to establish when and in what way cortical properties in the two groups develop to the final adult state.

Several studies have pursued this approach, usually restricting their attention to animals younger than 6 to 8 weeks of age (Pettigrew 1974, Blakemore & Van Sluyters 1975, Fregnac & Imbert 1978, Bonds 1979, Derrington 1980). Most studies agree on the course of development beyond the age of about 4 weeks: after this time, cortical function in normal and deprived animals is clearly different. What remains unresolved is the question of the "starting point" for these developmental sequences, and thus the question of whether deprivation merely arrests development or causes atro-

phy. Those who find relatively large numbers of selective neurons in neonatal animals (Blakemore & Van Sluyters, Fregnac & Imbert, Bonds) report a slight decline in the quality of cortical function during deprivation. Those who find neonates to be in essence "undeveloped" (Pettigrew, Derrington) report little change with extended deprivation periods. Some results also suggest that there might be a brief period of passive maturation in BD animals. For example, Sherk & Stryker (1976), recording from 3½-week-old deprived kittens, report a very high proportion of orientation selective neurons. This age group is curiously poorly represented in most other studies, and it might be that passive maturation proceeds in both normal and BD animals until this time, after which development proceeds in normals while cortical function atrophies in deprived kittens. In addition, the anatomical observations of Cragg (1975b), which suggest that synaptic development is by no means abolished by deprivation, seem to argue against the idea that the cortex is simply "frozen" by deprivation.

Monkeys Since most reports on neonatal cortex tend to support some notion of innate wiring, it seems likely that deprivation causes actual atrophy. The sparse evidence available from experiments on young monkeys tends to support this view. Wiesel & Hubel (1974) reported that the cortex of the neonatal monkey is rather adult-like, but that even animals deprived for relatively short periods have a noticeable proportion of abnormally unresponsive or unselective neurons. And Crawford et al (1975) found that about half the cells studied in a monkey that had been binocularly deprived early in life were unresponsive to visual stimulation. In broad outline, then, the properties of cortical neurons in young monkeys and the way in which deprivation affects those properties appear similar to those in kittens.

Does binocular deprivation preserve cortical plasticity? Cynader et al (1976) found that relatively brief periods of visual experience in BD cats could restore large numbers of cortical cells to at least approximately normal function; this is in marked contrast to findings (discussed below) that similar recovery periods are ineffective in selectively deprived cats. Cynader (1979) presents evidence in favor of the intriguing idea that one of the effects of BD is to "freeze" in their neonatal state whatever mechanisms normally truncate the period of cortical plasticity; thus a 4- or 6-month-old BD animal might be as susceptible to environmental influence as a much younger normal animal. Cynader's evidence comes from experiments in which one eye of BD cats was opened at the age of 4 to 10 months; these animals showed shifts in cortical ocular dominance typical of younger monocularly deprived animals, and there is evidence that the effects can be seen within a few days or weeks of monocular experience. Since light-reared

cats monocularly deprived at the same age show less change in cortical eye dominance, these results can be interpreted as evidence that deprivation extends the "critical period" for cortical development.

EFFECTS OF SELECTIVE DEPRIVATION

> Ye that are of good understanding,
> note the doctrine that is hidden under the veil of the strange verses.
>
> —Dante, *The Divine Comedy, Inferno* IX, 61

In this section we turn to experiments involving more selective kinds of visual deprivation. A natural suggestion of the results of the complete deprivation experiments discussed above would be that selective kinds of visual deprivation might have selective effects. But how might these effects be mediated? It is possible to imagine that a particular kind of visual experience would be sufficient to induce development of a particular, presumably related, visual function, but that experience has no other effect than to "gate" otherwise normal development. However, there is abundant evidence from studies of several different kinds that selective experience exerts a much more active influence on development than this idea would suggest. Our second question is thus posed: in what way, and within what limits, does the visual environment act to modify neural function?

Monocular Occlusion

Wiesel & Hubel (1963b, 1965a) studied the cortical effects of periods of early unilateral eye closure in kittens. In marked contrast to the nonspecific atrophic changes that result from bilateral eye closure or dark rearing, monocular closure produces a pattern of physiological and anatomical changes in cortex that can only be explained by active modification of neural connection patterns. These cortical changes are accompanied by changes in LGN that appear to be secondary to changes in cortical afferent patterns.

VISUAL CORTEX After a period of unilateral eye closure, Wiesel & Hubel found that the great majority of cortical neurons (which in normal or BD animals may be activated through either eye) responded to stimulation only when it was delivered through the nondeprived eye. This does not result from a simple atrophy of neurons connected to the deprived eye, since recordings from the cortex of monocularly deprived (MD) animals reveal no sizable regions devoid of active neurons and no marked increase in the number of neurons that cannot be activated visually. These findings have been widely replicated (e.g. Blakemore & Van Sluyters 1974, Olson & Freeman 1975, Kratz & Spear 1976, Movshon & Dürsteler 1977). Using special techniques to record from the small neurons of layer IV, Shatz &

Stryker (1978) showed that there remain significant numbers of neurons in this layer that retain functional contact with the deprived eye; this observation apart, there has been no important addition to Wiesel & Hubel's original findings. In monkeys, MD has effects similar in form and magnitude to those seen in cats (Baker et al 1974, Crawford et al 1975, Hubel et al 1977, Blakemore et al 1978a).

Eyelid suture both abolishes spatially patterned retinal stimulation and reduces the amount of light entering the eye by several log units, but it appears that it is the loss of spatial pattern that is critical to the effectiveness of deprivation. Depriving an animal of vision with a translucent contact lens is as effective as lid suture in changing cortical ocular dominance, even when care is taken to match the total flux entering each eye (Wiesel & Hubel 1965a, Blakemore 1976). Conversely, reducing the amount of light entering the eye without abolishing pattern vision does not significantly shift eye dominance toward the nonattenuated eye (Blakemore 1976).

Geniculocortical and intracortical effects Two mechanisms appear to be involved in the cortical changes consequent to MD. The first involves a change in the sizes of the nonoverlapping ocular dominance bands devoted to the two eyes in layer IV. In MD animals, the bands devoted to the deprived eye fail to attain their normal extent, and the territory they eschew is invaded by enlarged bands devoted to the experienced eye (Hubel et al 1977, Shatz & Stryker 1978). Thus in layer IV, where geniculate terminals from each eye normally occupy about 50% of the available territory, the experienced eye comes to control 70–80%. This change alone, however, cannot explain the full extent of the cortical changes produced by MD. In normal animals, the eye that dominates a band of layer IV also dominates cells in layers above and below that band (Hubel & Wiesel 1965, 1968; Kennedy et al 1976; Hendrickson & Wilson 1979). In MD animals, however, virtually all cortical neurons outside layer IV respond only to stimulation of the experienced eye, even those that lie above and below the bands of remaining layer IV input from the deprived eye (Hubel et al 1977, Shatz & Stryker 1978). Thus a second mechanism, involving changes in intracortical rather than geniculocortical connectivity, must be involved. Further evidence for this comes from the fact that MD of late onset can cause significant overall changes in cortical ocular dominance without changing the size of layer IV ocular dominance bands (Hubel et al 1977).

A role for suppression? The first of these deprivation mechanisms—the reallocation of terminal space in layer IV—can be simply viewed as a change in the pattern of afferents that changes the ocular dominance of cortical cells by changing the balance of their excitatory input from the two

eyes. It is not clear that the second mechanism—changing intracortical connection patterns—operates so simply. There is evidence that in many cortical cells, inputs from the deprived eye are present but suppressed by a tonic inhibitory influence from the experienced eye. Kratz et al (1976) showed that removal of the experienced eye in adult MD cats caused an immediate increase in the proportion of cells that could be activated through the deprived eye. This finding has been confirmed by Hoffmann & Cynader (1977), Van Sluyters (1978), and Crewther et al (1978b), but remains controversial in view of negative findings by Harris & Stryker (1977), Blakemore & Hillman (1977) and Hawken et al (1978). A difficulty of interpretation arises, since the effects reported by Kratz et al are not dramatic, and the possibility exists that enucleating or otherwise inactivating an eye might have subtle effects other than purely visual ones on cortical responsiveness and on the probability of recording from different types of cell (see, for example, Crewther et al 1978b). Nevertheless, the body of evidence suggests that there is indeed a "release" phenomenon following enucleation; the natural explanation is that the experienced eye exerts a tonic inhibitory influence that is abolished when the eye is enucleated. There is evidence that the cells responding to the deprived eye after enucleation are found throughout cortex and are not confined to layer IV, suggesting that the effect must at least partly result from reorganization of intracortically relayed signals (Smith et al 1978).

Duffy et al (1976) reported that intravenous bicuculline (which blocks the action of GABA, a putative inhibitory neurotransmitter in cortex) causes a similar release effect. While this finding is consonant with the enucleation results, it must be noted that bicuculline has serious effects on structures outside the visual cortex and that the published data are not compelling. Singer (1977) reported on the basis of electrical stimulation experiments in deprived animals that intracortical inhibitory pathways appear less affected by MD than direct excitatory pathways. Also, Fiorentini & Maffei (1979) report that suitable averaging techniques reveal weak excitatory inputs from the deprived eye in a substantial proportion of neurons in MD cats. All these results are at least consistent with a role for a suppression mechanism in the cortical effects of MD, though none of them provide a basis for any detailed speculation on its nature or source.

Onset of deprivation effects The effects of brief periods of eye closure have been studied by Hubel & Wiesel (1970), Olson & Freeman (1975), Movshon & Dürsteler (1977), and Shatz et al (1977). During the fourth week of life, as little as one day of MD has marked effects on cortical binocularity. The first effect to appear is a radical reduction in the proportion of binocularly activated cells; after longer deprivation periods, a shift in ocular dominance

becomes obvious. The ocular dominance bands of layer IV become more sharply defined after brief periods of MD, without showing the changes in extent that occur after longer periods (Shatz et al 1977).

Sensitive period for deprivation effects The cortex is susceptible to MD during the first 4 months or so of a kitten's life; deprivation after that time has little or no effect (Wiesel & Hubel 1965a,b; Hubel & Wiesel 1970; Cynader 1979). Hubel & Wiesel originally reported that the "sensitive period" did not begin until the beginning of the fourth week, but Van Sluyters & Freeman (1977) showed that some susceptibility to deprivation effects is present even during the second week. The most sensitive point in the sensitive period occurs during the fifth week; thereafter, effects of a constant deprivation period are less and less marked.

The effects of MD may be partly or completely reversed within the sensitive period if the sutured eye is opened and the open one sutured. This reversed MD is capable of reversing cortical ocular dominance completely if performed before the age of 5 weeks; delaying reversal beyond this time decreases the rate and then the extent of cortical dominance changes (Blakemore & Van Sluyters 1974, Movshon 1976, Berman & Daw 1977). Blasdel & Pettigrew (1978) reported that the effectiveness of deprivation reversal depended on the duration of the initial deprivation as well as on the age at which reverse suture took place; this is not in agreement with some other findings (compare Movshon 1976 and Van Sluyters 1978). Estimates of the sensitive period obtained from deprivation reversal experiments agree well with those obtained from experiments on induction of deprivation.

Hubel & Wiesel (1970) found that the effects of deprivation were not lessened by a subsequent period of binocular visual experience, even within the sensitive period, but Mitchell et al (1977) and Olson & Freeman (1978) showed that the deprived eye may regain considerable influence in this way. This recovery, like the recovery induced by reversed deprivation, involves only the relative balance of the two eyes' inputs in cortex—few binocularly activated cells are seen after recovery, and many of these have receptive field properties that are poorly matched in the two eyes (Blakemore & Van Sluyters 1974, Movshon 1976, Mitchell et al 1977). Reversed deprivation is also effective in reversing the effects of MD in monkeys (Blakemore et al 1978a, LeVay et al 1979).

Binocular competition It is clear that the effects of MD are more extreme than one would predict from a knowledge of the effects of BD. This, combined with their results on kittens raised with artificial strabismus or alternate monocular occlusion (see below) prompted Hubel & Wiesel (1965) to propose that a developmental mechanism that depends critically on a

competitive interaction between the two eyes operates in the cortex. This idea has proved most helpful in understanding the effects of a number of environmental manipulations that affect cortical binocular interaction.

The idea of binocular competition is usually couched in terms of a battle among geniculate afferents for terminal space in the cortex. Initially, LGN input from either eye is supposed to be potentially affective; over time, the input that more often activates the postsynaptic neuron comes to dominate that neuron. This idea is reminiscent of Hebb's (1949) model of learning in neural circuits; an ingenious biophysical explanation has been offered by Stent (1973).

The data available in 1965 did not fully specify a model of binocular competition, since there was no evidence that postsynaptic neurons needed to be involved for competitive effects to be seen. Four studies have recently attempted to answer this question by manipulating the visual input in such a way as to differentially activate pre- and postsynaptic elements.

Singer et al (1977) and Wilson et al (1977) devised a situation in which there would be asymmetric presynaptic activity but little or no postsynaptic activity: they raised animals under conditions of BD, but stimulated one eye with temporally modulated diffuse illumination. Since geniculate cells respond well to diffuse light but cortical cells do not, any ocular dominance shift would have to be due largely to presynaptic activity. Neither study reported a shift, and both concluded that postsynaptic involvement was a necessity.

Cynader & Mitchell (1977) and Rauschecker & Singer (1979) offered other evidence that cortical activity was necessary for ocular dominance to shift. Both groups stimulated one eye of kittens through a strong cylindrical lens that blurred contours of one orientation while correctly focusing those at the orthogonal orientation, by this means hoping to take advantage of the orientation selectivity of cortical cells to dissect cortical from geniculate-based effects. Cynader & Mitchell raised their kittens giving the other eye normal visual experience, while Rauschecker & Singer first deprived one eye and then reverse-sutured them, exposing the second eye through the cylindrical lens. Both groups sought, and found, an orientation-dependent change in ocular dominance: cells sensitive to the orientations correctly focused through the cylindrical lens tended to be dominated by the eye having the lens; cells sensitive to other orientations often were dominated by the other eye. Since only the postsynaptic cortical cells would distinguish on the basis of orientation, both groups again concluded that postsynaptic involvement was critical.

While the results of these four studies clearly suggest that the effects of MD occur primarily in cortex rather than in the LGN, it is less clear that they demonstrate that *postsynaptic* involvement is essential. If all cortical

cells were orientation selective, binocularly driven and monosynaptically driven by LGN afferents, this conclusion would be inescapable; since they are not, however, it is not. All studies assume that the pattern selectivity of cortical cells (either their insensitivity to diffuse light or their orientation selectivity) and the convergence of binocular signals on these cells occur together; the analysis depends on pitting one of these properties against the other *across one synapse.* However, it appears that simple cells receiving direct geniculate input are often monocularly driven (Albus 1975, Shatz & Stryker 1978); only complex cells and simple cells outside layer IV tend to be binocularly activated. Thus it is conceivable that the results of these studies could be explained by two entirely presynaptic competitive interactions, first one between LGN fibers for control of layer IV, and then a second between the outputs of layer IV cells for control of cells in other layers. This bears an obvious conceptual similarity to the two mechanisms implicated in other MD studies (see above); as in those studies, definitive conclusions must await a laminar analysis of effects, with particular attention to the small cells of layer IV analyzed by Shatz & Stryker (1978). None of the four studies in question provides such an analysis.

Two other studies have partially pattern-deprived one eye. Eggers & Blakemore (1978) raised kittens with spherical blurring lenses over one eye; they observed a decrease in the spatial resolution of receptive fields driven through the blurred eye compared to those driven through the unblurred eye. Similar results, obtained in the LGN of kittens deprived by the rather less well-controlled means of chronic application of atropine by Ikeda & Tremain (1978b) suggest that, unlike the effects discussed above, these results may reflect changes in more peripheral parts of the visual pathway.

LATERAL GENICULATE NUCLEUS Three effects of MD have been reported in the LGN. Cells in the deprived layers of the nucleus are smaller than those in experienced layers; Y cells are more rarely encountered in recording from deprived layers than in normal layers; there may be a spatial resolution deficit in X cells recorded in deprived layers.

Morphological effects Wiesel & Hubel (1963a, 1965a; Hubel & Wiesel 1970) noticed that cells in deprived layers of the LGN tend to be 30–40% smaller in cross-sectional area than cells in experienced layers. Guillery (1973) and Garey et al (1973) showed that this results from a retardation of growth among cells connected to the deprived eye; cells connected to the open eye may grow faster and attain slightly larger size than cells in normal cats (Wan & Cragg 1976, Hickey et al 1977).

Wiesel & Hubel originally believed that the cell size differences were caused by a reduction in retinal signals afferent to the deprived LGN

neurons and were unrelated to the changes they found in cortical binocularity. Subsequent work, however, strongly suggests that a binocular competition mechanism is involved in the LGN changes. The most parsimonious view appears to be that this is in fact the same competition mechanism seen in cortex, exerting retrograde effects in LGN.

Cell size differences are prominent only in regions of the LGN representing the binocular visual field. Guillery & Stelzner (1970) found no differences in cell size between cells representing the monocular segment of the visual field in MD animals, and Guillery (1972) made similar observations on cells representing a so-called "critical segment" of the visual field produced by making a retinal lesion in the nondeprived eye. Hickey et al (1977) reported some cell-size differences in the monocular segment of the LGN of long-term MD cats, but these changes are small in magnitude, late in onset, and generally similar to those seen throughout the LGN following BD (Guillery 1973, Hickey et al 1977). In monkeys, the difference between binocular and monocular segments of the LGN in their response to MD is somewhat less marked (von Noorden & Middleditch 1975), but cell growth seems more affected by BD in this species than in the cat (Headon & Powell 1978, Vital-Durand et al 1978).

The relative sizes of cells in the different layers of the LGN are well correlated with cortical ocular dominance, especially when changes in cortical dominance are effected in such a way as to change the size of the ocular dominance bands in layer IV (e.g. Sherman et al 1974, Garey & Dürsteler 1975, Dürsteler et al 1976, Movshon & Dürsteler 1977, Vital-Durand et al 1978). Moreover, the time course of the onset of LGN cell-size changes, and of their reversal by reversed deprivation, is indistinguishable from the time course of effects seen on cortical binocularity and ocular dominance column size (Dürsteler et al 1976, Wan & Cragg 1976, Cragg et al 1976, Movshon & Dürsteler 1977). Finally, abnormalities of LGN cell size are unaccompanied by changes in synaptic development that are normally associated with anterograde degeneration effects (Winfield et al 1976).

These findings are all consistent with the notion that LGN cell size is determined by the success with which a particular cell makes contact in the cortex; this success is often determined by a binocular competition mechanism (see above). Retrograde effects of this sort are well known in other neural systems (e.g. Lund 1978, Jacobson 1978).

It appears that all relay cells in the LGN are affected by deprivation but that larger cells show more marked effects than smaller ones (Hoffmann & Holländer 1978). By injecting HRP into areas 17 and 18 of MD cats, Garey & Blakemore (1977) and LeVay & Ferster (1977) showed that the large presumptive Y cells projecting to area 18 are much more affected by deprivation than the mixed population of cells projecting to area 17. In addition,

LeVay & Ferster (1977) and Lin & Sherman (1978) report some reduction in the number of labeled cells in deprived layers of the LGN following cortical injections.

Loss of Y cells Sherman et al (1972) reported that the frequency with which Y cells were encountered in recordings made from deprived LGN layers was much lower than it was either in normal animals or in the nondeprived layers of MD animals. This finding has been confirmed a number of times (Hoffmann & Cynader 1977, Hoffmann & Holländer, 1978, Sireteanu & Hoffmann 1979, Eysel et al 1979), and is not apparent in recordings made from the retina of MD animals (Sherman & Stone 1973).

While it is tempting to infer from these results that deprivation exerts a specific influence on the development of the retino-cortical Y pathway, several factors complicate the interpretation. Microelectrodes are more likely to record from large than from small cells, and deprivation causes marked cell-size changes in parts of the LGN coextensive with the zones in which Y cells are "lost" (see above). If the largest LGN cells are Y cells, and these are most changed in size after MD (LeVay & Ferster 1977, Garey & Blakemore 1977), then the Y cell "loss" could simply result from changes in recording probability. No definitive statement is possible on this point, since the determinants of microelectrode selectivity are not well understood: different laboratories using techniques that should produce similar results report wildly varying proportions of Y cells in LGN recordings, even in normal animals (cf Hoffmann et al 1972, So & Shapley 1979).

There is some evidence for a genuine loss of Y cells, or at least of functionally active Y cells, in BD animals where there is little abnormality of cell size (Sherman et al 1972, Kratz et al 1979b). Moreover, Kratz et al (1978), studying the medial interlaminar nucleus of the LGN (MIN), which contains almost solely Y cells, report large changes in recording probability and significant numbers of abnormal cells after MD. On the other hand, Eysel et al (1979), while confirming the Y cell loss in geniculate recordings, were unable to find any loss of Y cells in recordings made from the optic radiation between LGN and cortex. Recently Shapley & So (1980) have been unable to verify the Y cell loss, even in recordings made from LGN.

Certain other data are not easy to reconcile with an extensive Y cell loss. Area 18, which in cat receives its main LGN input from Y cells, is in some respects *less* affected by deprivation than area 17 (Singer 1978). In monkeys, where the Y cells are segregated into the magnocellular layers of the LGN (Dreher et al 1976), there is no evidence for special effects of MD on these layers (Headon & Powell 1973, von Noorden & Middleditch 1975). On balance, until more evidence is available about the cortical terminations of

the X and Y pathways, and the way these terminations are affected by deprivation, it will be difficult to assess the significance of the reported selective effects of MD on Y cells.

Resolution deficits in X cells Less well resolved even than the effects of MD on LGN Y cells is the status of reports that the spatial resolution of X cells (the other major cell type in the dorsal layers of the LGN) is markedly decreased by deprivation. Maffei & Fiorentini (1976a) claimed that LGN spatial resolution was roughly halved in deprived layers; while they did not classify their cells as X or Y, subsequent reports suggest that their results were due to changes in X cells rather than Y cells (Lehmkuhle et al 1978, 1980; Sireteanu & Hoffmann 1979).

The nature and magnitude of these changes are not well established. Maffei & Fiorentini and Lehmkuhle et al report resolution changes of about 50%, while Sireteanu & Hoffmann find a 30% difference between deprived and nondeprived layer A and no effects in layer A_1. Moreover, Derrington & Hawken (1980) and Shapley & So (1980) find no effect at all of deprivation on spatial resolution.

Kratz et al (1979a) report that retinal X cells are unaffected by deprivation, suggesting that, like the Y cell "loss," X cell resolution deficits in MD cats are of geniculate rather than retinal origin. This contrasts oddly with Ikeda & Tremain's (1979) report that an X cell resolution loss in esotropic strabismus (see below) is of retinal origin.

It is impossible to draw firm conclusions from these new and mutually contradictory reports. There is, however, a plausible optical reason for some of the resolution deficits in deprived cats. Lid suture, as mentioned above, causes deficits in eye growth and corneal formation that can produce high myopia in sutured eyes (Wiesel & Raviola 1977, Gollender et al 1979). While refractive errors are of course corrected during electrophysiological experiments, the powerful negative lenses needed cause a significant image minification. Rough calculations suggest that this might be as large as 20–25%, and could thus account for a significant portion of the effect reported. Unfortunately, none of the papers reporting resolution losses details the refractive state of the cats' eyes.

Summary Monocular occlusion and its many variants are as well studied as any developmental manipulation. The main effects of these procedures are seen in cortex, with retrograde influences on the morphology and possibly the physiology of the LGN. Within cortex, two mechanisms seem to be involved, one that is a competition between geniculate afferents for terminal space in layer IV, and a second, possibly involving intracortical suppression, that exerts its primary influence outside layer IV.

Artificial Strabismus

Hubel & Wiesel (1965) described the changes in cortical function produced by raising kittens with their visual axes artificially misaligned in mimicry of the common human clinical condition of strabismus. Several months of divergent strabismus (exotropia, produced by disinserting the medial rectus muscle) beginning near birth reduces the proportion of cortical neurons receiving excitatory binocular input from around four-fifths to less than one-fifth; receptive field properties other than binocularity are apparently unaffected. These findings have been widely confirmed (Wickelgren-Gordon 1972; Yinon et al 1975; Yinon 1976a; Blakemore 1976; Ikeda & Tremain 1977; Blakemore & Eggers 1978, 1979; Van Sluyters & Levitt 1980) for both exotropic and esotropic (convergent) strabismus.

Cortical ocular dominance columns in strabismic cats are remarkably well defined both physiologically and anatomically (Hubel & Wiesel 1965, Shatz et al 1977). In fact, Hubel & Wiesel's observation of regular periodic variations in eye dominance in these animals led them to reexamine their data from normal animals and propose the existence of ocular dominance columns as a feature of normal cortical organization.

Interocular asynchrony Hubel & Wiesel reasoned that misalignment of the visual axes causes an absence of synchrony in the signals falling on corresponding retinal points; this decorrelation of the signals in the cortical afferent pathways from the two eyes could cause connections to a cortical cell from the eye less effective in activating that cell to weaken and disappear through a competitive interaction of the sort discussed above. Additional evidence for this idea came from experiments in which kittens were alternately monocularly deprived, day by day: this alternate occlusion causes a breakdown in cortical binocularity indistinguishable from that seen after strabismus (Hubel & Wiesel 1965). Recently, Blasdel & Pettigrew (1979) tried to measure the amount of interocular asynchrony needed to disrupt cortical binocularity; they found that the alternating periods of occlusion each had to last many seconds before binocularity was disrupted. Blasdel & Pettigrew note that this seems rather longer than the period that Hubel & Wiesel's model would predict, but they did not systematically study the most important parameter for testing this model, the duration of the blank interval between stimuli delivered to the two eyes.

Alternatives to the interocular asynchrony hypothesis Thus far, the evidence we have considered on factors causing a breakdown of cortical binocularity is all consistent with an idea that esssentially visual aspects of the rearing situation account for the effects observed. In recent years evidence of several kinds has accumulated that nonvisual influences on the develop-

ment of binocular interaction may be of some importance. Ideas of this sort are as yet rather ill defined but fall into two groups: that somehow proprioceptive signals from the extraocular muscles can influence cortical binocularity; or that the effectiveness of visual signals in controlling behavior modulates some aspects of visual cortical development.

Evidence on the role of visuo-motor integration has come from experiments on the effects of torsional strabismus produced by rotating the eye surgically about its visual axis. Blakemore et al (1975b) found that unilateral 90° eye rotation caused a decrease in cortical binocularity similar to that observed after more usual forms of strabismus; this result, of course, can be readily understood within a binocular competition framework and has been replicated by Yinon (1975, 1976b). Oddly, if the unrotated eye is occluded by lid suture, the open, rotated eye fails to take control of sizable numbers of cortical neurons; rather, many cells become unresponsive or unselective and remain binocularly driven (Yinon 1975, 1976b, 1977a,b; Singer et al 1979b). One obvious possibility is that the eye rotation surgery, which is rather extreme, somehow disturbs the retina or optic nerve and thus compromises visual signals from the operated eye. Singer et al (1979b) attempted to control for this possibility by doing "sham" surgery on two kittens by disinserting all the extraocular muscles (a necessity in all eye rotations), but leaving the eyeball in its "normal" orientation in the orbit. In these kittens, eye dominance shifted toward the open, operated eye, as would be expected from conventional MD results.

Singer et al suggest that their results can best be explained by assuming that the degree to which visuo-motor integration is disrupted by an environmental manipulation importantly influences cortical development. Eye rotation, which is held to disrupt visuo-motor integration, thus leaves cortex relatively unaffected; sham rotation, held to be less disruptive, allows the cortex to respond in the usual way to abnormal experience. This scheme is, however, difficult to reconcile with behavioral data showing that kittens can execute complex visual-motor tasks using a rotated eye alone even if the normal eye was not occluded during development (Mitchell et al 1976a, Gordon et al 1979a, Peck et al 1979).

More direct evidence that altered visuo-motor function does not affect cortical development comes from the results of Freeman (1978), who subjected kittens to daily alternate monocular occlusion, allowing them normal mobility while one eye was open but restraining them while the other was open. This completely disrupts visuo-motor integration through the "passive" eye (Hein et al 1970), yet Freeman found no tendency for that eye to lose control of cortical neurons.

We thus return to the idea that the most parsimonious explanation of the failure of monocular occlusion to affect cortical dominance in eye-rotated

cats is to be found in the hypothesis that the surgery is often locally disruptive, and that such cats are effectively subjected to a form of visual deprivation in the rotated eye. The eye rotation experiments thus become understandable within a conventional framework, without the necessity of postulating nonvisual influences. This notion finds further support in a brief report by Crewther et al (1978a), showing that ocular dominance in bilaterally eye-rotated kittens was identical to that found by others in normal or BD kittens. We should note that this is most certainly not the interpretation favored by these authors, who believe their results indicate it is the relative balance of proprioceptive signals from eye muscles in the two orbits that is critical.

This idea may be traced to a series of experiments by Maffei and his co-workers, in which the claim is presented that proprioceptive signals are of paramount importance in determining cortical ocular dominance (Maffei & Bisti 1976; Maffei & Fiorentini 1976b, 1977; Buisseret & Maffei 1977; Maffei 1978). In one experiment, kittens were made strabismic by disinserting muscles in one or both eyes. If the strabismus was asymmetric, cortical binocularity was lost, but symmetrically induced strabismus was ineffective. In a second study, unilateral strabismus was produced in kittens that were then given BD for some months; binocularity was lost in these kittens despite the fact that visual experience was apparently prevented. The findings of Crewther et al (1978a) discussed above, showing that bilaterally eye-rotated kittens have normal cortical binocularity, can be taken in conjunction with those of Blakemore et al (1975b) showing that unilateral eye-rotation kittens lose binocular cells, to provide support for the "proprioceptive imbalance" idea. And Freeman & Bonds (1979) showed that manipulation of the eye can increase the effectiveness of a brief period of MD in paralyzed kittens.

On closer examination, however, this idea seems less compelling. First, many of the findings upon which it is based have not proved to be replicable. Both Singer et al (1979c) and Van Sluyters & Levitt (1980) report that bilaterally produced strabismus is as effective as unilateral strabismus in reducing cortical binocularity. Van Sluyters & Levitt also failed to find a decrease of binocularity in strabismic kittens briefly deprived of vision; they further note that prolonged BD *alone* has been reported to reduce cortical binocularity (Wiesel & Hubel 1965a, Kratz & Spear 1976), allowing an alternative explanation for Maffei & Bisti's (1976) results.

Other results are also difficult to reconcile with the proprioceptive imbalance theory. Van Sluyters (1977, Van Sluyters & Levitt 1980; see also Smith et al 1979) has shown that an optical strabismus produced with prism-containing goggles is as effective as surgical strabismus in reducing cortical binocularity, despite the lack of involvement of proprioceptive mechanisms.

And others (e.g. Hirsch & Spinelli 1970, Shinkman & Bruce 1977, Blasdel & Pettigrew 1979) have presented results showing that other interocular stimulus differences, also unaccompanied by any obvious proprioceptive abnormality, can break down binocular connections. Conversely, Blakemore (1976) reported that exposure designed to match the visual images in the two retinae might preserve binocular connections in strabismic cats; the status of this observation is, however, doubtful (Blakemore 1976, p. 442).

It thus appears that interocular differences in patterned retinal stimulation are both *necessary* and *sufficient* to produce the full range of changes observed in the cortex of strabismic kittens, and that proprioceptive imbalance alone is not *sufficient* to produce these effects. It is more difficult to judge the *necessity* of proprioceptive abnormalities, since most procedures that involve disparate stimulation of the eyes result in a failure of eye alignment (e.g. Blake et al 1974) that might conceivably also involve changes in proprioceptive signals. But this is speculation, and in the absence of clear positive evidence it seems wise to doubt the importance of proprioceptive influences on cortical binocularity.

Anomalous retinal correspondence Two reports claim a significant adaptive change in cortical receptive field properties following strabismus resembling the clinical condition of anomalous retinal correspondence, in which the oculocentric visual direction of the deviating eye is shifted so that it approaches that of the other eye. Buchtel et al (1975) immobilized one eye of adult cats and claimed to observe large compensatory shifts in the receptive field locations of cortical cells. However, the data are not presented in any detail, and the logic behind a fixed shift in receptive field position as compensation for a variable (noncomitant) strabismus is obscure. Shlaer (1971) raised kittens wearing goggles containing prisms that produced a small (about 2°) vertical misalignment of the visual axes. He claimed on the basis of a small sample of neurons that binocular cortical receptive fields had shifted position so as to compensate for about half this deviation; it is doubtful that Shlaer had sufficient information about eye movements in his recording situation to support this claim, even if his cats did not (as seems likely) make small vertical fusional eye movements to compensate for the prisms without altering retinal correspondence.

Van Sluyters (1977) examined these issues: he found that kittens raised with small vertical prismatic deviations showed normal cortical binocularity without a measurable shift in receptive field position; larger deviations reduced cortical binocularity, again without shifting the receptive fields of the few remaining binocular neurons.

There is one other report of an unusual change in receptive fields following strabismus. Singer et al (1979a) found that horizontal strabismus re-

duced the proportion of cells in striate cortex responding to vertical contours and horizontal image movements. They interpret these results in terms of the possible role of these cells in the control of fusional vergence eye movement, obviously absent in strabismic animals.

Strabismic amblyopia Humans with strabismus often have greatly reduced visual capacity in the deviating eye. An analog of this strabismic amblyopia was reported by von Noorden & Dowling (1970), who found that acuity was much reduced in the deviating eye of rhesus monkeys given artificial esotropia near birth. Examination of the LGN in these animals showed that cells in layers receiving input from the deviated eye were smaller than those connected to the normal eye (von Noorden 1973, von Noorden & Middleditch 1975), and recordings from visual cortex revealed that few cells could be activated through the deviated eye (Baker et al 1974). These findings are similar to those reported by others to follow monocular occlusion, and different in character from the reported consequences of strabismus in cats discussed above.

Evidence for strabismic amblyopia in the cat came from Jacobson & Ikeda (1979), who showed a severe resolution deficit in the deviating eye of esotropic cats. A correlate of this behavioral loss is found in the LGN where cells, especially X cells, show gross deficits in spatial resolution (Ikeda & Wright 1976). The severity of this loss decreases as age of onset of the strabismus increases, suggesting that esotropia simply arrests the development of geniculate X cell spatial resolution (Ikeda et al 1978). This resolution loss is reminiscent of that reported to occur in geniculate X cells following MD (see above), but differs in that it is restricted to X cells representing the central visual fields. Moreover, Ikeda & Tremain (1979) reported a similar loss of resolution in retinal *area centralis* X cells in esotropic cats, while the retina is apparently unaffected by MD (Kratz et al 1979a).

In addition to decreased acuity, esotropic cats have severely constricted nasal visual fields in the deviating eye (Ikeda & Jacobson 1977, Kalil 1977). A physiological correlate of this field loss is found in the LGN, where cells in layer A_1 ipsilateral to the deviating eye are smaller than cells in layer A or cells in the contralateral LGN (Ikeda et al 1977), and in the striate cortex where there is a tendency for the nondeviating eye to control an increased proportion of neurons (Kalil et al 1978).

The severe spatial resolution deficits Ikeda and co-workers find in the peripheral visual pathways are difficult to reconcile with reports that esotropia, like exotropia, reduces cortical binocularity without altering the spatial characteristics of receptive fields (Yinon 1976a; Blakemore & Eggers 1978, 1979; Kalil et al 1978). This apparent conflict may be resolved on the

basis of a procedural difference. Ikeda's method for producing esotropia is idiosyncratic—she finds it necessary to extirpate two extraocular muscles, the nictitating membrane and connective tissue at the lateral canthus to produce a large-angle, long-duration deviation. Blakemore & Eggers simply disinserted a single muscle, the conventional method for producing artificial strabismus in cats (e.g. Hubel & Wiesel 1965, Kalil et al 1978, Van Sluyters & Levitt 1980). Indeed when Ikeda attempted to replicate her resolution deficits using the conventional surgical technique, she failed (Ikeda & Tremain 1979). It should also be noted that the techniques used in monkeys by von Noorden and his colleagues (see above) are also rather extreme; both his and Ikeda's methods appear likely to produce a serious ocular paresis as well as the simple deviation (without serious loss of ocular motility) that results from disinserting a single muscle.

Even if surgical differences can account for the different results obtained in esotropia, it is difficult to understand why even paretic strabismus should have even more serious effects on the retina and LGN than complete deprivation does (cf for example Ikeda & Wright 1976, Lehmkuhle et al 1980). Certainly Ikeda's suggestion that image blur resulting from accommodative errors in the deviating eye is the causative factor seems unlikely, and the possibility must be considered that the extreme nature of her surgical techniques can result in damage to the eye or orbital tissues sufficiently severe to cause pathological damage by itself.

Sensitive period for the effects of strabismus Yinon (1976a), Van Sluyters (1977), and Ikeda et al (1978) have studied the age-dependence of the effects of artificial strabismus of various types in cortex and in LGN. From their results it appears that the "sensitive period" for the effects of strabismus is identical to that for monocular occlusion (see above).

Restricted Pattern Exposure

Neurons in the visual cortex have three properties absent in the LGN: binocularity, orientation selectivity, and direction selectivity (Hubel & Wiesel 1962, 1968). Experimental manipulation of binocular visual input by means of monocular occlusion, strabismus, and the like affects the development of binocularity in cortex; we now consider the effects of manipulations of visual pattern inputs upon cortical stimulus selectivity.

STRIPED ENVIRONMENTS Blakemore & Cooper (1970) and Hirsch & Spinelli (1970, 1971) raised kittens in environments in which visual experience was limited to contours of a single orientation; both groups reported an alteration in the distribution of orientation preferences in cortex, with more cells preferring orientations near the experienced orientation than

other orientations. This finding has recently been the center of some controversy, both over the magnitude and even the existence of the effect, and over its implications for mechanisms of cortical development.

The nature of stripe-rearing effects There are important differences between the results of Blakemore & Cooper and Hirsch & Spinelli, which are obscured by the idiosyncratic method used by Hirsch & Spinelli to analyze cortical unit properties. Blakemore & Cooper found that in their kittens, cells having normal receptive field properties were recorded with a frequency and regularity not diminished from normal—the only important effect of stripe-rearing they noted was the altered distribution of orientation preferences. Hirsch & Spinelli, on the other hand, found that most cells in their animals were not selective for orientation. To be sure, those that *were* orientation selective matched the orientations used in rearing, but were a minority.

Interpretation of these differences is complicated by the fact that the two groups performed importantly different experiments. Blakemore & Cooper raised their kittens with both eyes open in cylinders painted with stripes—in this situation, rotation of the head and changes in gaze might significantly change the *retinal* orientation exposure. Hirsch & Spinelli used goggles to expose patterns to their otherwise dark-reared kittens—this procedure fixes retinal orientation more accurately than cylinder-rearing does, but removes any correlation between self-produced movements and changes in the retinal image. Moreover, Hirsch & Spinelli's kittens saw vertical contours through one eye and horizontal contours through the other. This led (presumably for simple reasons of uncorrelated binocular stimulation, see above) to a breakdown of binocularity in addition to a change in the cortical orientation preference.

Even when methodological differences are taken into account, there are real differences between the two groups' findings. These suggest two interpretations of the effects of stripe-rearing, which borrow from the cortical consequences of either MD or BD. Hirsch & Spinelli's results seem best explained by an "atrophy" model based on the results of BD experiments: in this model, cells that initially preferred orientations absent in the rearing situation are effectively deprived and show the same poverty of sensitivity and selectivity as cells in BD cats. Blakemore & Cooper's results, however, are more consistent with a "modification" model conceptually similar to the binocular competition idea used to explain the effects of MD: since in their results all cortical cells prefer orientations similar to those present in the rearing situation, it must be that neurons initially disposed to prefer other orientations are "captured" by the exposure, in a manner analogous to the capture of cortical territory by the open eye in an MD animal.

Neither report contained sufficient data or detail to distinguish between these models; this requires detailed information about the magnitude of the effect, and especially about the number and cortical distribution of cells that either prefer orientations different from the rearing orientation or prefer no orientation at all. The wide variation among the results of later studies makes a definitive answer elusive.

Blakemore and his co-workers have continued to report both very strong biases in the distribution of preferred orientations and a very small proportion of unresponsive or unselective neurons in stripe-reared animals of various kinds (Blakemore & Mitchell 1973; Blakemore 1974; Blakemore & Van Sluyters 1975; Blakemore 1976, 1977; Blakemore et al 1978b). This view has received limited support from other laboratories (Pettigrew et al 1973b).

Hirsch and his colleagues have continued to report sizable numbers of nonoriented or unresponsive neurons in stripe-reared cats (Spinelli et al 1972, Leventhal & Hirsch 1975, Stryker et al 1978).

Several other groups have reported biases in the distribution of cortical orientation preference following stripe-rearing that are neither as extreme as those found by Blakemore nor accompanied by as high a proportion of abnormal cells as found by Hirsch (Blasdel et al 1977, Flood & Coleman 1979, Gordon et al 1979b; see also Spencer 1974, Turkel et al 1975, Tretter et al 1975, Cynader et al 1975, Freeman & Pettigrew 1973).

Finally, two reports have claimed to find no orientation bias following stripe-rearing (Stryker & Sherk 1975, Fiorentini & Maffei 1978); one of these (Stryker & Sherk) is noteworthy for its use of "blind" experimental procedures and automated receptive field analysis techniques. Both these studies used cylinder-reared animals; no negative findings from goggle-rearing experiments have come to our notice.

Despite this plethora of reports, few address the questions of cortical functional architecture that are critical. Stryker et al (1978), who studied kittens reared in goggles in the manner of Hirsch & Spinelli, analyzed the sequences of preferred orientation encountered in their electrode penetrations according to the methods devised by Hubel & Wiesel (1974). This revealed that in the regions of the penetrations where receptive fields sensitive to orientations not seen during rearing would be expected, nonoriented and unresponsive cells were found. This is, of course, the result predicted by the "atrophy" model. On the other hand, Blakemore (1976) shows a penetration reconstruction that appears more consistent with a "modification" model. But few reports show distributions of orientation preference sufficiently tight to rule out explanations in terms of biased samples and "missed" cells during recording, and the available evidence appears to favor the "atrophy" model over the "modification" model of the effects of stripe

rearing. This also has the virtue of parsimony, in that we may offer explanations of the effects of partially and completely restricted visual experience in essentially the same terms, postulating no special additional mechanism of plasticity to deal with stripe-rearing results.

OTHER UNUSUALLY PATTERNED ENVIRONMENTS A third sort of explanation for the effects of early exposure to specific patterns proposed an even more extreme form of modification than that suggested by Blakemore & Cooper. In this scheme, cortical neurons are held before visual experience to be *tabulae rasae,* upon which the visual environment may imprint almost any stimulus preference. Evidence for this could most obviously come from the generation by visual experience of definite stimulus preferences in cortical cells for stimuli not preferred by cells in normal animals. Some anecdotal evidence of this kind emerged from stripe-rearing studies (Spinelli et al 1972, Pettigrew & Garey 1974, Spinelli 1978), but a more definite test would be to change the properties of a group of cortical cells in such a way that they are both indisputably mature and also different from cells seen in normal animals. Attempts of this sort were made by Pettigrew & Freeman (1973) and Van Sluyters & Blakemore (1973), who raised kittens in environments composed of small, randomly scattered spots of light, in the hope that cortical cells might develop a spot preference (rarely found in normal animals). While both reports claimed positive results, the data are sparse, normal control animals absent, and no quantitative measures of sensitivity (especially necessary for this sort of experiment) are shown. Moreover, Blakemore & Van Sluyters (1975) reinterpret their data in a more general context as consistent with the notion that experience of extended contour is necessary for normal cortical development; this emphasizes that evidence for cells both distinctive and mature in these kittens is lacking.

RESTRICTED EXPERIENCE OF IMAGE MOTION Direction selectivity, like orientation selectivity and binocularity, appears in cats and monkeys at the level of the striate cortex. This property is present in neurons recorded from young kittens lacking visual experience (Hubel & Wiesel 1963, Barlow & Pettigrew 1971). Attempts of two kinds have been made to modify cortical direction selectivity: rearing animals under conditions of "directional deprivation" by giving them experience only of intermittently illuminated visual scenes, and attempting to bias the distribution of direction selectivity by exposing animals to patterns moving in only one direction.

Motion deprivation Cynader et al (1973) and Olson & Pettigrew (1974) studied the effects of rearing kittens in an environment illuminated strobo-

scopically at a low rate (less than 1 Hz); the idea here is that ample experience of pattern will be available without retinal image motion. A simple prediction would be that cortical direction selectivity might be selectively impaired; in fact, very low rates of stroboscopic illumination appear to have effects as severe as total pattern deprivation, and animals raised in this environment have few orientation or direction selective cortical neurons. A more selective effect on directionality was reported by Cynader & Cherneko (1976), who raised their kittens in stroboscopic illumination at the rather higher rate of 8 Hz. This appears to leave the spatial receptive field properties of cortical cells unaltered, but radically reduces the proportion of directionally selective neurons.

Unidirectional rearing Several groups have raised kittens in a controlled environment in which contours move in one direction only; despite the obvious problems of stimulus control posed by natural eye and head movements, all report positive results (Cynader et al 1975, Tretter et al 1975, Daw & Wyatt 1976). In these kittens, about three quarters of direction-selective neurons prefer movement in the experienced direction. Tretter et al used moving stripe environments in their study; not surprisingly, they report finding a bias in the distribution of preferred orientation as well as the directional bias. Initially more surprising is the similar finding of Cynader et al, who used moving "blobs" rather than stripes. However, if one considers that only the edges of the "blobs" oriented orthogonally or nearly orthogonally to the direction of movement were in fact in motion on the retina during rearing, this finding becomes explicable in conventional terms.

The effects of unidirectional rearing appear quantitatively less dramatic than the more extreme results reported to follow stripe-rearing, in that many cells remain functional with stimulus preferences different from those satisfied by the rearing environment. Given the problems of stimulus control during rearing (all directional rearing studies used free-field stimuli rather than goggles), it is difficult to ascribe strong significance to this difference.

SENSITIVE PERIOD FOR THE EFFECTS OF SPECIAL PATTERNS Blakemore (1974) studied the effect of age on the effectiveness of periods of stripe-rearing; his data are consistent with the idea that the sensitive period for the induction of these effects is identical to that for the induction of the effects of monocular occlusion and strabismus (see above).

Daw and his colleagues have, however, provided some evidence that the sensitive period for the effects of unidirectional rearing ends rather earlier than that for the effects of MD (Daw & Wyatt 1976, Berman & Daw 1977).

Daw et al (1978) provide the most compelling evidence for this idea in an experiment that pits the reversal of lid suture against the reversal of unidirectional rearing; they show that reversed lid suture at the age of 5 weeks can reverse cortical ocular dominance, but that reversing the directional environment at the same time does not effectively reverse the cortical distribution of direction preference. If both manipulations are performed in the same kitten, cortical neurons are strongly dominated by the *second* eye to be open, but tend to prefer movement in the *first* direction seen; about 10% of cortical cells combine these two preferences.

Daw's results raise the interesting possibility that there may be different sensitive periods for the development of different neuronal properties; we may expect more studies of this sort (perhaps on sensitive periods for the development of disparity or spatial frequency selectivity) in the future.

Acute Conditioning of Cortical Unit Properties

Claims that very brief periods of abnormal visual experience can have marked effects on visual function have been made for a number of experimental situations, including monocular occlusion (Hubel & Wiesel 1970, Olson & Freeman 1975, Movshon & Dürsteler 1977, Freeman & Olson 1979); artificial strabismus (Van Sluyters 1977); stripe-rearing (Blakemore & Mitchell 1973); and unidirectional rearing (Tretter et al 1975). The effectiveness of a few hours or days of deprivation in awake, freely moving animals prompted a number of studies in which attempts were made to alter cortical unit properties acutely, during electrophysiological recording experiments (Pettigrew et al 1973a, Pettigrew & Garey 1974, Imbert & Buisseret 1975). The exciting prospect that the dynamics of cortical plasticity could be studied directly by this means has, however, receded in recent years.

There are several difficulties in evaluating the results of these studies. The initial reports contained rather little data and little evidence of awareness of the very large response variability in young animals. Moreover, several recent attempts to reproduce short-term conditioning effects have failed (Stryker & Sherk 1975; Freeman & Bonds 1979 and their note 2). For a time it seemed that a period of "consolidation" during which the mechanisms of plasticity would act to alter neural function might be needed (Pettigrew & Garey 1974, Peck & Blakemore 1975); subsequent work has shown, however, that a delay between brief exposure and recording dilutes rather than enhances the effects (Olson & Freeman 1975, Freeman & Olson 1979).

If brief periods of exposure are effective in awake, freely moving animals but not in immobilized, anesthetized ones, it is natural to examine the effects of anesthesia and paralysis separately. Freeman & Bonds (1979) report that

brief exposure periods can be effective in anesthetized, paralyzed animals if artificial eye movements are provided, but it should be noted that their results are consistent with the idea that it is simply necessary that the animal be aroused during the exposure period. While it is not in doubt that brief periods of experience can be developmentally effective, the early promise that this fact could be used effectively to study mechanisms of plasticity has not been fulfilled.

Catecholaminergic Regulation of Cortical Plasticity

In a series of provocative papers, Kasamatsu & Pettigrew (1976, 1979; Pettigrew & Kasamatsu 1978; Kasamatsu et al 1979b) have advanced the hypothesis that the degree to which abnormal visual input can affect cortical function is determined by monoaminergic pathways originating in the brainstem (Moore & Bloom 1978, 1979). It is clear that factors other than purely visual ones influence cortical plasticity: most obviously, the susceptibility of the cortex to environmental influence varies with the age of the animal (see above). In addition, regulation of cortical plasticity by brainstem mechanisms could explain the apparent dependence of environmental modifiability on arousing or more specific ascending activity (see above).

Kasamatsu & Pettigrew's first observations suggested that intraventricular administration of 6-hydroxydopamine (6-OHDA), a neurotoxin specific to monoamine-containing neurons, prevented the cortical eye dominance shift after a period of monocular occlusion. This by itself is not conclusive, since 6-OHDA has many effects on brain function and behavior that could produce essentially pathological effects. Later they refined their techniques and used intracortical rather than intraventricular perfusion, which is anatomically highly specific (Kasamatsu et al 1979a); the results were similar.

Their second experiment (Pettigrew & Kasamatsu 1978, Kasamatsu et al 1979b) was more persuasive. They performed a pharmacological substitution study and showed that local cortical perfusion of norepinephrine (NE, the monoamine neurotransmitter they believe to be involved) could restore cortical modifiability even in the presence of intraventricular or intracortical 6-OHDA; Kasamatsu (1979) provided evidence that noradrenergic β-receptors mediate this effect. While some of Kasamatsu & Pettigrew's claims concerning the ability of intracortically perfused NE to extend the period of plasticity into adulthood (Kasamatsu et al 1979b), and the ineffectiveness of catecholamines in affecting cortical response to reversed lid suture (Ary et al 1979), seem less well founded, their experiments have demonstrated a mechanism that may regulate cortical modifiability. How

this system operates, and whether it is merely one of several neural subsystems that modulate plasticity, are questions that await further study.

GENETIC AND ENVIRONMENTAL INFLUENCES ON VISUAL DEVELOPMENT

> To a greater force, and to a better nature, you, free, are subject,
> and that creates the mind in you, which the heavens have not in their charge.
>
> —Dante, *The Divine Comedy, Purgatorio* XVI, 79

In our survey we have considered evidence from a variety of sources demonstrating that the visual environment plays a crucial role in the development of visual function. Despite some evidence for environmental effects on the retina and LGN, it is in the visual cortex that the most striking and interesting effects are seen.

A simple model of cortical development might regard the role of environmental influences in terms of the simple "functional validation" of connection patterns innately laid down. Thus the devastating effects of visual deprivation would represent a validation failure, and the partial development seen under conditions of partial visual deprivation would reflect a combination of normal development of connections adequately validated with the loss or atrophy of others. Certainly this model is consistent with the evidence that at least the skeleton of the normal organization of cortical receptive fields appears to be present before visual experience, with the effects of BD, and probably also with the effects of rearing in specially patterned environments. But it accounts less well for many of the changes seen after rearing under conditions that disrupt binocular function. For example, the clear capture of cortical territory by the open eye in an MD animal cannot reflect only a simple "deletion" of inappropriate connections; a compensatory expansion of other connections is certainly involved.

A second model would allow the environment more actively to guide the formation of functional connections; this model could be posed in a variety of versions differing in the range of guiding power permitted the environment. While current evidence suggests that this role is smaller than was thought a few years ago, we cannot consider it to be negligible.

A strong prediction of the "functional validation" model is that neurons in the visual cortex should either develop normal function or should fail in varying degrees to attain it—they should certainly *not* develop specific functional properties different from those innately laid down. Yet there is widespread evidence that cortical neurons can acquire unusual properties

of a special kind: distinct but different stimulus specificities when stimulated through the two eyes. In normal cats, binocularly driven cortical neurons have closely matched receptive field properties in the two eyes (Hubel & Wiesel 1962). In particular, the preferred orientations in the two eyes never differ by more than 15° (Blakemore et al 1972, Nelson et al 1977). Yet cats raised under conditions in which the two eyes are never stimulated together sometimes possess abnormal cortical neurons having widely disparate orientation preferences in the two eyes (Hirsch & Spinelli 1971, Blakemore & Van Sluyters 1974, Leventhal & Hirsch 1975, Movshon 1976, Stryker et al 1978). These neurons may be few in number, yet their presence indicates that environmental influences can induce marked changes in neuronal properties. Indeed there is evidence that in some cases in which these neurons are found, wholesale changes in the functional architecture of the cortex can occur (Blakemore 1976, Movshon 1976).

On these grounds, a strictly constructed validation model may be rejected. But if the environment does have some shaping influence, what role does it play in normal animals? An appealing idea has its roots in the persistent involvement of binocular interaction in most areas in which extensive plasticity may be demonstrated, and in the apparent ease with which normal binocular function may be disrupted. This idea holds that mechanisms of binocular combination require a flexibility greater than innate predispositions can supply, and that the visual environment provides essential information that guides their development (Pettigrew 1978, Blakemore 1979). There is certainly ample evidence for modifiability of binocular connections, and it appears that effects even on receptive field properties other than binocularity are most clearly seen after rearing conditions that also affect binocularity (e.g. Hirsch & Spinelli 1971, Movshon 1976, Stryker et al 1978, Gordon et al 1979b).

It seems plausible, then, that the main structural plan of the cortex is innately drawn, but that the environment, in addition to validating that plan, actively contributes to the development of binocular function. But plausibility is not certainty—what *is* certain is that continued active research in this field will refine, and perhaps render obsolete, the concepts that are with us today.

> Therefore the sight that is granted to your world penetrates within
> the Eternal Justice as the eye into the sea;
> for though from the shore it sees the bottom, in the open sea it does not,
> and yet the bottom is there but the depth conceals it.
>
> —Dante, *The Divine Comedy, Paradiso* XIX, 73

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