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Development of the Geniculocortical Pathways

S. Murray Sherman

Dr. Guillery has already touched on the use of animal models, particularly cats and monkeys, to study the neural basis for certain forms of amblyopia. I would like to continue this with the addition of a perspective which is slightly different, namely a consideration of what the functional properties of individual neurons from visually deprived cats tell us about the neural substrates of amblyopia. For the purposes of this presentation, functional properties of individual neurons are determined by receptive field analysis as outlined in Figure 1. Typically, an anesthetized animal is placed in front of a projection screen and a fine microelectrode is guided next to a single neuron in the visual system. The electrode monitors the neuron's electrical activity as visual stimuli are moved or flashed on the screen. The stimulus parameters (such as the localized area of the screen or retina, the shape and motion of the targets, etc.) that cause the neuron to become active, define that neuron's receptive field. In the case of binocular neurons, which are common in the visual cortex, a nearly identical receptive field can be mapped for each eye.

In animal studies of amblyopia, this analysis has been applied most frequently to cats raised with one eye sutured closed, so it is useful to consider again the cat's visual pathways. Figure 2 shows the retino-geniculo-striate pathways of the cat, and they are, in most respects, quite like those of humans. The lateral geniculate nucleus (LGN) is laminated, as drawn in a frontal section, and we shall focus our attention on the top two laminae: A and A1. In normal cats lamina A receives its input from the contralateral nasal retina, and A1, from the ipsilateral temporal retina. These LGN cells are monocular since they have receptive fields for only one eye, and receptive fields of geniculate neurons are quite like those of their retinal inputs. But notice that there is a convergence in the geniculo-striate pathway such that the cortical neurons are typically binocular. There is another important difference besides binocularity between receptive fields of LGN and those of cortex. For geniculate cells, the receptive fields are small and circular in configuration, and almost any

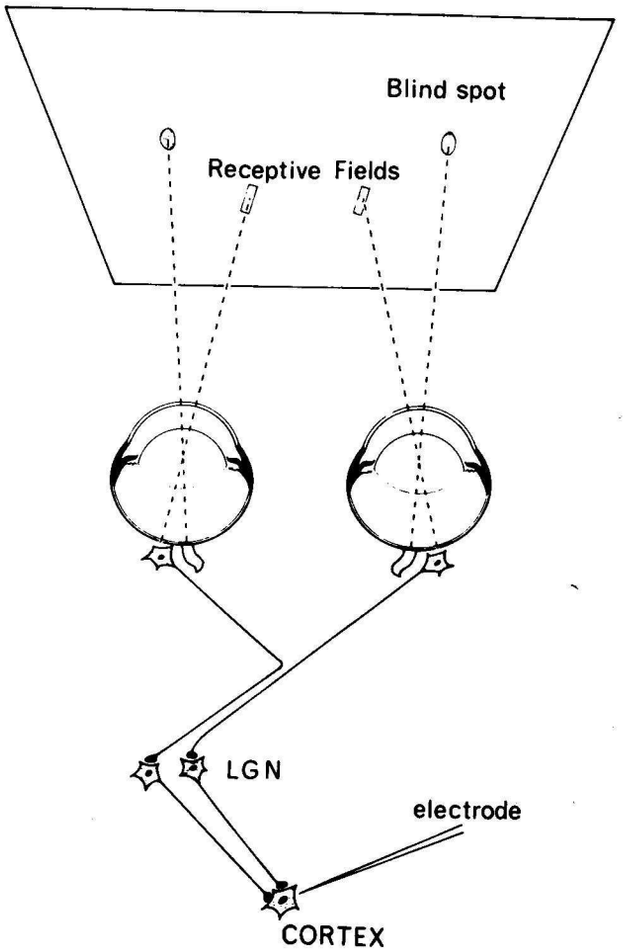

Figure 1: Schematic of physiological preparation to study receptive fields. The animal is paralyzed and the eyes face a frontal tangent screen on which retinal landmarks (i.e., optic discs, etc.) are projected through the nodal points. A fine microelectrode is positioned near a cell in the lateral geniculate nucleus (LGN) or visual cortex, and in this way the action potential activity of a single neuron is monitored. This activity can be changed by appropriate visual targets correctly placed in or moved through a small region of the tangent screen, and this defines the receptive field of the cell. This receptive field can also be transferred to retinal coordinates. A cell can have a receptive field in one or both eyes.

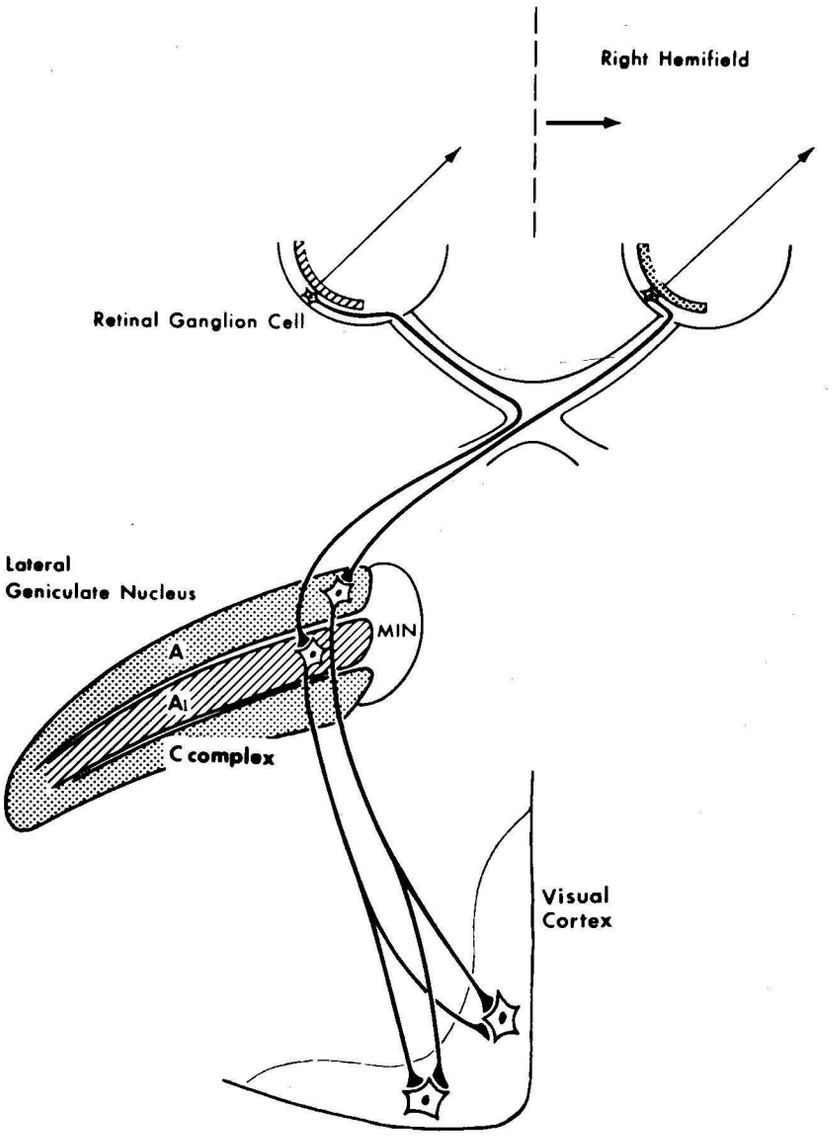

Figure 2: Diagram of the cat's retino-geniculo-striate pathways. Note the individual laminae of the lateral geniculate nucleus, each of which receives input from only one eye, and the convergence onto binocular cortical neurons from monocular geniculate cells.

flashing or moving target regardless of shape will activate the cell. For cortical cells the receptive fields tend to be elongated, and activation of the cell requires that the target be similarly elongated along the correct axis. In other words, target orientation becomes a critical receptive field parameter for cortical neurons, and each cell will respond only to a limited range of target orientations. Of course, among all cortical cells all target orientations are represented, otherwise we would be blind, like an astigmat with meridional amblyopia for certain axes.

Now that the normal cat's visual pathways have been briefly described in functional terms, we can consider their status after rearing with the eyelids of one eye sutured closed. Figure 3 summarizes this for retina, LGN, and striate cortex. Dr. Guillery has described much of this. Among other things, Figure 3 divides the pathways into binocular and monocular segments, and this can be readily done for the LGN and striate cortex because of the precision of the point-to-point map of the retina found in these structures. Like us, the cat has a large area of central visual field which is seen by either eye (this is the binocular segment), and has peripheral crescents seen only by the eye on that side (these are the monocular segments). In the LGN, the binocular segment includes all of lamina A1 and the adjoining lamina A, because neurons here have receptive fields in the binocular segment of visual field; the same argument applies to the lateral third of lamina A that extends beyond A1--- this is the monocular segment. A similar distinction is made in striate cortex.

Figure 3 summarizes the results of monocular deprivation. In this example, the left eye has been sutured. Therefore, the deprived laminae of the LGN are A1 on the left and A on the right.

The cat's retina seems to develop fairly completely despite the lid suture, although subtle deficits cannot yet be ruled out. Therefore, the most serious effects we relate to amblyopia occur central to the retina, probably in the geniculostriate pathways.

As expected, nondeprived laminae of the LGN develop quite normally, but deficits have been noted for the deprived laminae. The cells there are abnormally small and deficient receptive field properties are encountered. An interesting feature seen at the LGN, as Dr. Guillery has told you, is that these deprivation anomalies are virtually limited to the binocular segment. The deprived monocular segment, as

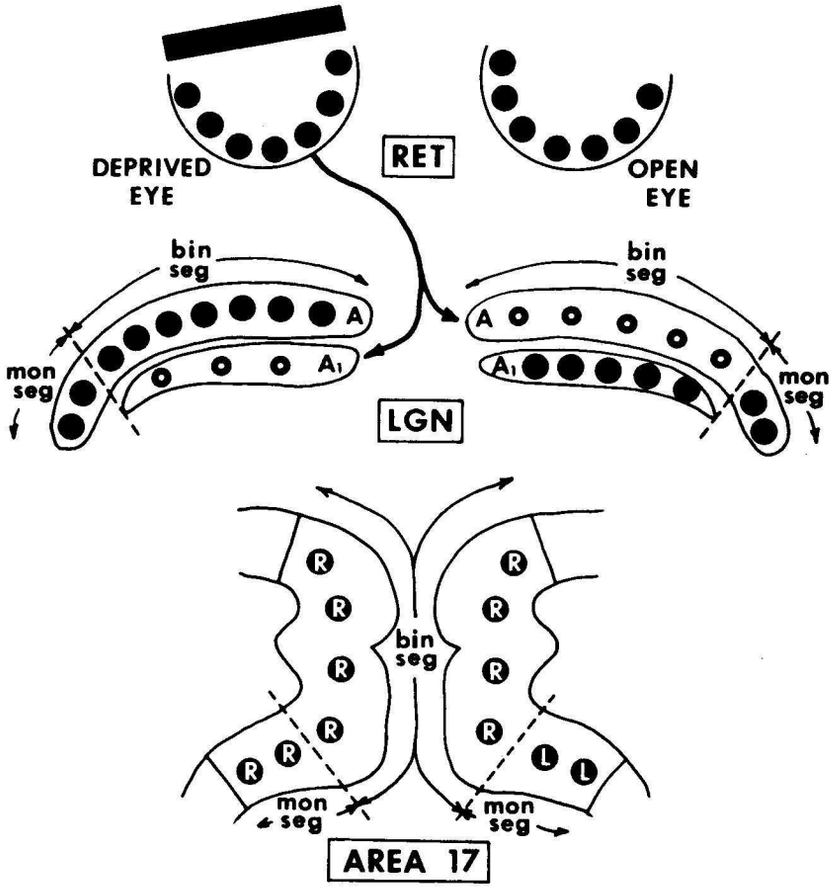

Figure 3: Summary diagram of the effects of left monocular deprivation on the development of the retino-geniculo-striate pathways (see text). The deprived retina develops fairly normally but deprived geniculate laminae do not: cells there are smaller and functionally abnormal. In cortex, instead of the normal pattern of binocular receptive fields, cells can be influenced only by the nondeprived (right) eye. These geniculostriate defects are largely limited to the binocular segment (where the central, binocularly viewed portion of visual field is mapped), since the deprived monocular segments develop relatively normally.

indicated in Figure 3, has cells of normal size and receptive field properties.

The cortical effects of the deprivation are even more dramatic. Remember that in normal cats, nearly all cortical cells are binocular. As Figure 3 shows, nearly all of the cells in the binocular cortical segment, after monocular deprivation, are associated only with the nondeprived eye. That is, these cells have no receptive fields for the left (deprived) eye but do for the right (nondeprived) eye. It's as if functional connections from deprived geniculate laminae are missing in these cells. As in the LGN, however, these effects are largely limited to the binocular segment since many neurons in the deprived monocular segment (in the right hemisphere of this example) have normal receptive fields for the deprived (left) eye.

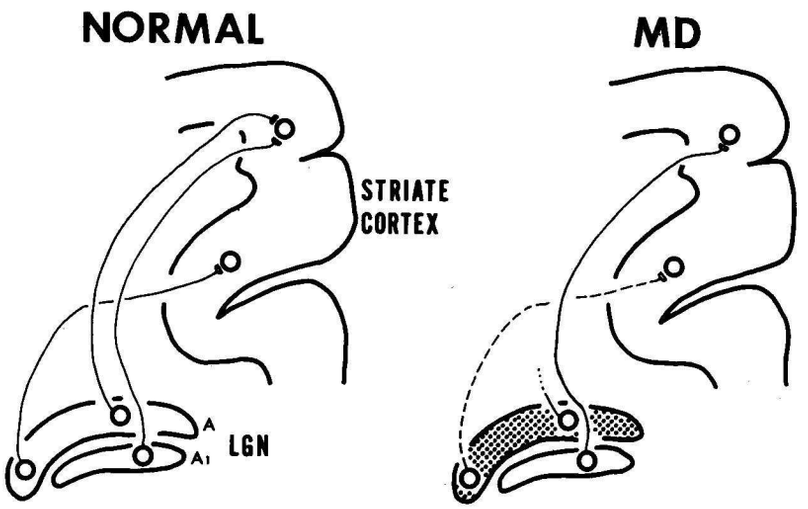

Figure 4: A possible mechanism of binocular competition during development. It is emphasized that the site and specific synaptic processes involved are largely unknown, and this example is hypothetical and used strictly for discussion purposes. See text for details.

One clear conclusion that can be drawn from these studies is that the binocular segments of the visual system are more susceptible to early deprivation than are the

monocular segments. Dr. Guillery has made this point and has suggested the underlying cause. That is, a form of competition exists during development between central pathways related to each eye, and therefore the battle ground is limited to the binocular segment. This "binocular competition" is further illustrated with a specific example in Figure 4 which was suggested by Wiesel and Hubel nearly 15 years ago. This competition could occur among geniculocortical synapeses in their attempt to dominate the cortical neurons. For instance, the left half of Figure 4 depicts normal development without deprivation. Imagine a tremendous postnatal proliferation in the number and/or strength of these geniculocortical synapses. As they develop, they compete with one another to dominate the cortical cell. However, on average, no subset of these synapses is blessed with a competitive advantage, so a balance is struck, and binocular neurons emerge. The right half of Figure 4 depicts development during closure of the contralateral eye (so that the neurons in lamina A are deprived and thus less active). (MD = Monocularly Deprived) Imagine that the same developmental mechanisms apply. Now during the competitive proliferation of geniculocortical synapses, those from the deprived lamina are at a distinct disadvantage, presumbaly due to their relative inactivity. This allows the synapses from the nondeprived eye to develop total domination of the cortical neurons. Now, however, if we consider a deprived neuron in the monocular segment---remember this neuron is as deprived and inactive as its neighbor in the binocular segment---we immediately see that there is no nondeprived neuron with which it must compete for develeopment of effective geniculocortical synapses. Thus it might develop at a slow rate due to its lack of activity, and it does not develop completely normally. However, this deprived neuron in the monocular segment does develop much better than its deprived neighbor in the binocular segment, primarily because it is not placed in a competitive situation. This, in any case, is the hypothesis used to explain the pattern of abnormalities seen in the geniculocortical pathways. Such a mechanism may well play an important role in the development of certain human amblyopic conditions.

However, an alternative explanation has been offered as to why the monocular segment developed better than did the binocular segment for the deprived eye. That is, we appreciate that visual acuity in the periphery (i.e., the monocular segment) is rudimentary compared to that near the fovea (i.e., the binocular segment). The pathways representing peripheral vision and the monocular segment may

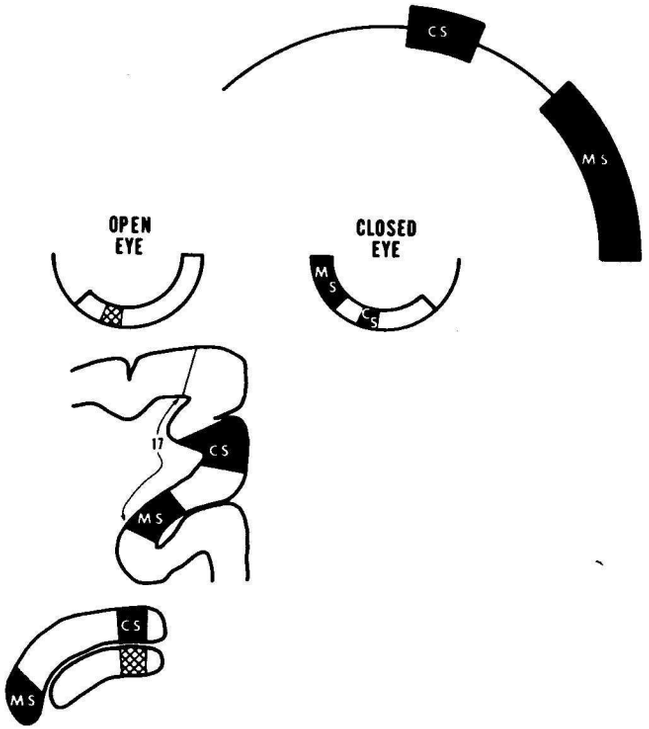

Figure 5: Critical or artificial monocular segment preparations (see text). At the time the right eye is neonatally closed, a small lesion is placed in the left retina. This creates two monocular segments relative to the deprived eye: a natural one (MS) and an artificial one (critical segment, CS). Both segments develop in the same way, and this supports the concept of binocular competition during development.

therefore simply be less sensitive to a non-optimal visual environment during development. Thus, they could develop more normally than pathways representing central vision and the binocular segment. That is, the observed differences of deprivation upon the binocular and monocular segments might be due to central/peripheral differences and not to binocular/monocular ones as suggested by the binocular

competition hypothesis. Dr. Guillery has designed an elegant experiment to test this latter explanation. I have worked with him on some of the experiments. This is the "critical segment" or "artificial monocular segment" preparation shown in Figure 5. Here one eye (the right) is sutured at the same time a small lesion is placed centrally in the retina of the open (left) eye. Now we have two monocular segments related to the deprived eye during development: the natural one associated with extreme nasal retina, and the artificial one homonymous with the other eye's lesioned retina and related to fairly central visual field. In all ways, the artificial and natural monocular segments develop in the same fashion. That is, behaviorally with the deprived eye, these cats respond to visual targets only in those portions of visual space related to the natural and artificial monocular segments: The scotoma selectively excludes these areas. In the deprived LGN lamina, only in the natural and artificial monocular segments did neurons develop normally. Cells with receptive fields for the deprived eye could only be found in the natural and artificial monocular segments in striate cortex. These studies strongly implicate some developmental mechanism of binocular competition. At least this is true for cats, and preliminary evidence suggests it applies to monkeys and probably to humans as well.

There is one last feature concerning the animal studies of amblyopia I would like to discuss. The concept of an early critical period for visual development is becoming increasingly important in the clinic. This is certainly a topic with which you are well versed, and the cat studies probably confirm your expectations. That is, practically all of the aforementioned abnormalities---including LGN development and the deprived eye's failure to influence cortex---are brought about in the cat if and only if the visual deprivation occurs in the first few postnatal months. This is the critical period. Even a few days of unilateral lid closure during the middle of this period can lead to significant and permanent geniculostriate abnormalities. No extent of deprivation after the critical period produces clear abnormalities. Figure 6 illustrates one of the ways the critical period was measured for kittens by Blakemore and Van Sluyters. These histograms show the relative frequency of binocular and monocular cells in striate cortex. Note that for the normal cat (and, incidentally, the neonate kitten as well), nearly all of the cortical cells are binocular. After monocular suture of the right eye throughout the critical period, as shown here, nearly all cells are influenced exclusively by the nondeprived left eye.

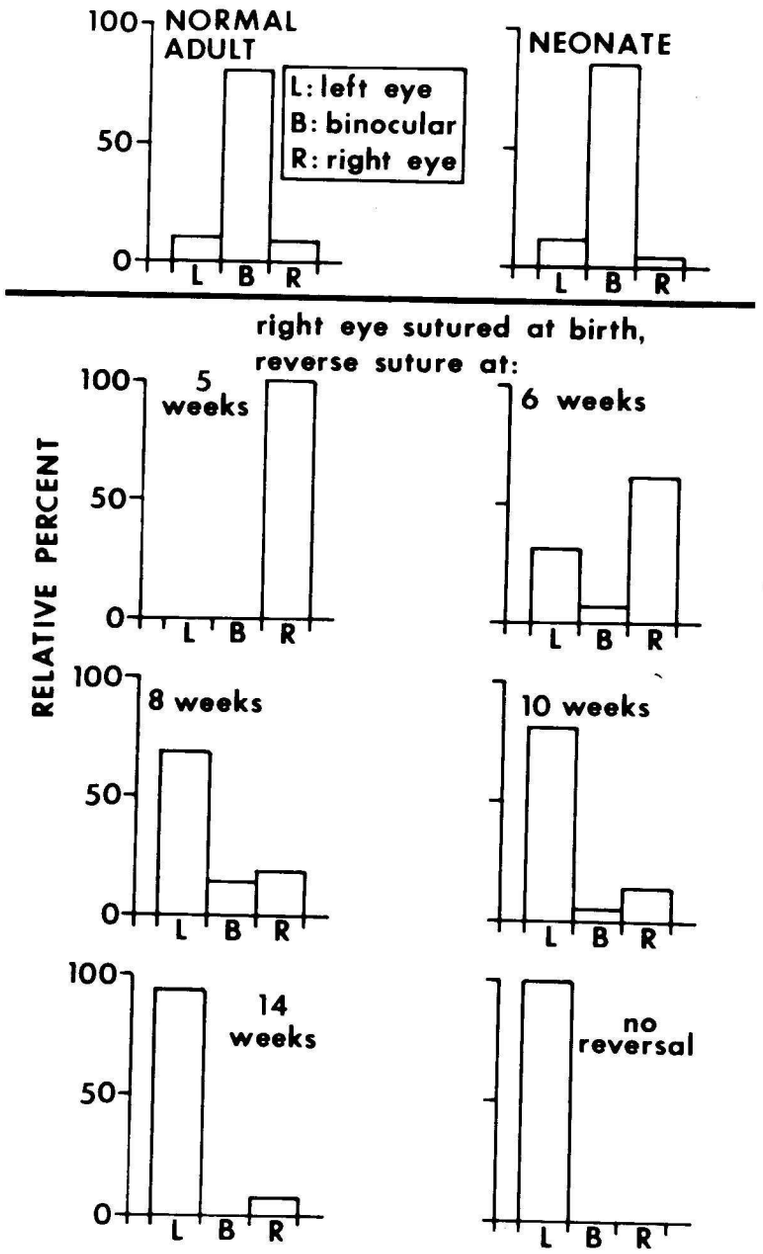

Figure 6: Cortical ocular dominance histograms of cats which have been reverse sutured at various ages, compared to normal cats and cats raised without reverse suture (redrawn from Blakemore and Van Sluyter, 1974). These data help define the critical period for cats.

The remaining histograms show what happens after a reverse-suturing technique at various ages. That is, the right eye is sutured at birth, and after a variable number of weeks indicated on each histogram, the right eye is opened and the left eye is shut. If this reversal occurs early in the critical period, nearly all cortical cells are controlled by the right eye, since it is opened for the bulk of that period; conversely, if the reversal is late, the left eye dominates cortex. Interestingly, intermediate times provide each eye with significant cortical input, but normal binocular responses are lost. That is, the cells are monocularly influenced, and each eye controls its own group separately. Not only does this figure illustrate the concept of an early critical period by defining the postnatal time during which the reverse suture is effective, but it also shows that development of normal binocular neurons requires a binocular visual environment. Of course, the human critical period seems to be measured in years instead of months, but what little evidence we have suggests that the same basic principles apply equally in humans and cats.

To conclude, I would like to describe a recently discovered amblyopia in humans that illustrates many of these points. This refers to the meridional amblyopia reported by Ralph Freeman and his associates at the University of California at Berkeley, and I shall cover it briefly. If an astigmat receives an appropriate optical correction early in life (i.e., by roughly 3 years of age), then, when tested as an adult with lines or gratings of various orientations, he displays normal visual acuity for all axes. This of course requires that he have the appropriate optical correction during testing. If, on the other hand, an astigmat does not receive optical correction before his teenage years, he develops a clear meridional amblyopia. That is, when tested even with optical correction, it is found that acuity is normal for all axes except one. This amblyopic axis is related to the defocused axis during uncorrected astigmatism, and the extent of the amblyopia is related to the extent of the astigmatism. Since the amblyopia can be demonstrated despite complete optical correction of the astigmatism, it must have a neural basis. Two points are illustrated here. First, the critical period is evident, since early optical correction of the astigmatism prevents the amblyopia. Second, the amblyopia itself seems to result from a deprivation effect limited only to certain cortical neurons. Remember that the overall population of cortical neurons responds to all stimulus orientations, but that each neuron responds only to a limited orientation range. During early astigmatism, most axes are maintained in good focus, so that

individual neurons sensitive to these axes receive normal stimulation and develop properly. However, the neurons sensitive to the axis which is out of focus are visually deprived and they fail to develop normally. This presumably is the neural basis of the meridional amblyopia, and our detailed understanding of it can be traced directly to experiments with cats. In most other cases, we are much further from explaining clinical phenomena with laboratory results. However, work on amblyopic animals continues at a rapid rate in many laboratories, and progress in this area during the next few years promises to be quite exciting and relevant to the clinician.

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A Primate Model for Amblyopia*

Gunter K. von Noorden

The previous papers have described exciting new advances with respect to the normal and abnormal development of the retino-geniculo-striate system in cats. The purpose of this paper is to supplement this information by summarizing our work on the primate visual system and discussing its clinical implications.

In order to simulate clinical conditions that are known to cause amblyopia in humans, infant macaque monkeys were treated either with unilateral or bilateral lid closure, were made esotropic or exotropic by appropriate surgery on the extraocular muscles, or were made anisometropic with unilateral lens extraction or constant unilateral cycloplegia. The results of behavioral experiments in some of these monkeys were discussed during the Bielschowsky lecture that I presented to this society eight years ago.[1] These data showed that the clinical characteristics of amblyopia in the rhesus monkey are similar to those in humans, thus establishing the validity of this model for further experimentation.

The ensuing work can be summarized as follows: unilateral lid closure, experimental esotropia and anisometropia in infant macaque monkeys cause a predictable set of behavioral, neurophysiologic and neurohistologic anomalies for which we suggested the term visual deprivation syndrome.[2] The neurophysiologic manifestations of this syndrome are as follows: recording extracellularly with microelectrodes from the striate cortex of amblyopic monkeys, we found a marked reduction of neurons that normally respond to stimulation from both eyes and of those that received input from the visually-deprived eye. In other words, a significant shift of cortical neuronal dominance in favor of the non-deprived eye had occurred.[3,4]

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Histological comparison of cells in deprived and non-deprived layers of the lateral geniculate nucleus (LGN) showed cell shrinkage in both parvo- and magnocellular deprived layers of the nucleus.[5] Light- and electronmicroscopic comparisons between the retinas from normal and amblyopic eyes showed no significant difference after unilateral lid closure for as long as one year. However in one monkey who had the right eye occluded from birth for a two-year period we found a decrease in the number and density of parafoveal but not of the peripheral retinal ganglion cells in the deprived eye.[6]

These behavioral, neurophysiological and histological consequences of abnormal visual stimulation could be elicited only in infant monkeys during a period of life that ranged from birth to approximately three months. The visual system of older animals was virtually immune to lid closure or artificial strabismus. During this sensitive period which has its counterpart in man, brief periods of abnormal visual stimulation were sufficient to cause the visual deprivation syndrome. For instance, we demonstrated that unilateral lid closure for only two weeks during the first seven weeks of life causes a significant reduction of visual acuity in the adult animal.[7] Only one week of unilateral lid closure or of experimental esotropia during infancy was sufficient to cause neurophysiological anomalies in the visual cortex that were comparable in severity to those occurring after long-term deprivation. In the LGN the changes appeared more gradually, indicating that differences may exist between the susceptibility of cortex versus LGN to visual deprivation. This difference also became apparent during reversal experiments. When suturing the previously non-deprived eye during the sensitive period, most cortical units now responded to stimulation of the previously deprived eye, whereas the histology in the LGN had been merely normalized without being reversed.[8] Thus, the severity of cortical and geniculate changes does not necessarily go hand in hand. Whether this discrepancy is merely caused by differences in the sensitivity of the electrophysiological versus the histological experimental approach, or indicates a primary cortical involvement, the geniculate changes occurring secondarily and at a later stage, needs to be clarified by further experiments.

The similarity of the cortical and geniculate anomalies in different forms of of experimental amblyopia suggests a common etiologic mechanism. In 1964, Jampolsky suggested that if the message from one retina is superior, the normal rivalry, or competition, between the two eyes may be upset,

and the superior message perceived more of the time.[9] He pointed out that the difference in clarity between the images in the two eyes during visual infancy may lead to far-reaching consequences. A similar concept was developed in neurophysiologic terms by Wiesel and Hubel[10] and by Guillery[11] who postulated that during the critical period of development the normal eye competes with the deprived eye, possibly for synaptic control of the central nervous system neurons. The LGN laminae connected with the deprived eye are at a disadvantage in this competition and the cells fail to reach normal size. The hypothesis of abnormal binocular competition was confirmed by Guillery[11] and by Sherman and his co-workers[12] in a series of elegantly designed experiments. These authors showed in cats that arrest of geniculate cell growth occurs only in those parts of the visual system where competitive interaction is anatomically possible, i.e. in the binocularly innervated LGN segment. We have fully confirmed this work in the monkey and were able to show an additional effect of visual deprivation, unrelated to binocular interaction, as cell shrinkage occurred, though to a lesser degree, also in the monocular segment of the LGN,[13] i.e. the part that receives input exclusively from the temporal periphery of the deprived eye's retina. This observation, together with the finding of retinal involvement after long-term deprivation, led us to conclude that form vision deprivation,, in addition to binocular interaction, contributes to the etiology of amblyopia.

The inference that similar structural and functional changes as described in experimental animals occur in humans after congenital cataract, esotropia or anisometropia is based so far on indirect evidence only. A histological study of the LGN from a human amblyopic patient has not been performed. However, amblyopia in its behavioral aspects is similar in monkeys and humans. In both species it occurs only during visual immaturity and not in adults, it develops with unilateral but not with alternating strabismus, and it can be reversed by enforced usage of the amblyopic eye. As the visual systems of humans and the macaques are structurally and functionally comparable, it is reasonable to assume that the structural and functional alterations observed in the visual system of experimental animals also occur in the brains of human amblyopes.

What are some of the clinical implications from this work? The experimental data have increased our awareness of the importance of an orderly visual environment in contributing to the development of innately present binocular visual functions. Any condition that may upset the delicate

functional balance between the input received from the two eyes during the sensitive period in life may cause alterations in the visual system that we are now able to define in structural and neurophysiological terms. Thus, we must avoid prolonged and uncontrolled occlusion or cycloplegia in one eye of infants and must correct anisometropia or high refractive errors as early in life as possible. Corneal opacities and congenital or traumatic cataracts during infancy have a similarly deleterious effect on normal visual development. We are now convinced that the unfavorable visual results from congenital cataract surgery in spite of greatly improved surgical techniques are caused by failure to operate and optically correct such children within their first few weeks of life.[14] We find no support for the frequently cited opinion that failure to obtain good vision in such children is usually the result of the coincidental association of congenital amblyopia with congenital cataracts.[15]

The period of susceptibility of the visual system to abnormal visual experience has been well defined by prospective experiments in many animal species. Such information is urgently needed for humans as well since we still do not know the upper age limit in chilren beyond which amblyopia is not likely to occur, nor do we know the minimal period of time during which abnormal visual input may be tolerated during the sensitive period or to what extent this tolerance varies during the different stages of this sensitive period. The only information at this time is that gleaned from retrospective analysis of individual cases and can be summarized as follows: (1) The age of sensitivity ranges from birth to approximately seven years and the degree of sensitivity varies from patient to patient. Reversibility of amblyopia is more likely to occur with an onset of visual deprivation toward the end of the sensitive period. (2) The degree of sensitivity appears to be greatest during the first two years of life and only brief periods of abnormal visual experience during this time are sufficient to interfere with normal visual development. (3) The adult visual system is immune to the effects of visual deprivation,.

It is of great clinical importance to narrow this gap in our knowledge. The collective experience of one clinician is insufficient to establish guidelines with the purpose of indicating, for instance, the urgency with which a traumatic cataract needs to be removed and the aphakic refractive error be corrected in the different pediatric age groups. The ISA, as a worldwide organization of physicians sharing a common interest, would be ideally suited to consider the

establishment of a registry for the collection and statistical evaluation of relevant clinical observations concerning the length of the sensitive period in humans and the minimal time of visual deprivation, that causes amblyopia during this period.

Finally, a word of caution is in order in interpreting the findings from animal experiments with respect to the management of congenital esotropia. We cannot automatically conclude that early surgical alignment of the eyes or maintenance of a balanced visual input by environmental modifications in children with congenital esotropia is sufficient to restore or maintain normal binocular functions. There is at this time no useful primate model available for the study of congenital esotropia. All information regarding the consequences of strabismus on function and morphology of the visual system in primate animal models has been based on artificial and often incomitant strabismus in animals with presumably normal innate binocular connections. We cannot exclude the possibility that a congenital defect of fusion is the cause of congenital esotropia as has been suggested many years ago by Claude Worth.[16] Indeed, the consistent postoperative finding of a monofixation syndrome with subnormal stereoacuity in congenitally esotropic children, regardless whether surgical alignment occurred during infancy or after the age of two, seems to support Claude Worth's theory. If this theory is correct, the age at which the eyes are surgically aligned is immaterial. If it is false, surgical alignment at the age of six months may well be too late and surgery at an even earlier age, or avoidance of any incongruous visual environment by other than surgical means may well restore completely normal binocular functions in these children.

These and many other unresolved questions remain to be answered by future investigation. This should not detract from the fact that the use of animal models for the study of strabismus and amblyopia has started a new and exciting area of research. Clinical investigations must continue, however, for a thorough knowledge of the human pathophysiology of strabismus and amblyopia is necessary in designing animal experiments in a manner that the conclusions are applicable to similar situations in man. Further progress in this field will depend on a close collaboration between basic scientists and research-oriented clinicians.

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