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Competitive Interactions Influencing the Development of Retinal Axonal Arbors in Cat Lateral Geniculate Nucleus

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I. INTRODUCTION

The development of the mammalian central nervous system reflects a sequence of events and processes of daunting complexity culminating in a mature system that is characterized by a high degree of connectional specificity. Within sensory projection systems, for example, this specificity is exemplified by the existence of "maps" and "patterns" in central structures. A large amount of data exists showing that central maps of sensory epithelia are highly ordered and relatively stable, suggesting a high degree of precision in the projection pattern of peripheral afferents onto central structures. Peripheral afferents also form orderly patterns in targets so that similar inputs are arranged together and are spatially distinct from dissimilar inputs. Finally, specific afferents connect to specific target cells, selecting particular cells and avoiding others. A fundamental task of developmental neurobiology is to understand how such precision and specificity is achieved.

We and others have chosen to address this problem by studying the development of retinal ganglion cell projections to the lateral geniculate nucleus (LGN). This review describes some experiments designed to characterize the mechanisms operating during that process, drawing chiefly from studies done in cats (and to a lesser extent, ferrets). We focus on the formation of patterns and cell-specific connections and address the issue in two ways. First, we review the process of laminar segregation of inputs from the two eyes and describe how different functional classes of afferents might play different roles in this phenomenon. Second, we describe the intralaminar development of retinal afferents and review data that suggest that competition between distinct classes of retinal afferents occurs during development. Finally, we address aspects of the available data that do not fit cleanly with either of those two sets of observations, but that nonetheless provide clues as to the identity and sensitivity of the mechanisms involved in retinogeniculate development. Before addressing

these themes, however, it is necessary to present an overview of the cat retina and LGN to provide a context within which to discuss the experimental results.

II. THE CAT RETINOGENICULATE SYSTEM

The retinogeniculate system of the cat is composed of at least three functionally distinct pathways arising from X-, Y-, and W-cells in the retina (for reviews, see Refs. 107, 116, 134, 135). These cell classes differ dramatically in their physiological properties, and their responses on a few key tests permit their classification with little or no ambiguity. Moreover, each of these functional cell classes is associated with unique morphological characteristics (4, 5, 27, 131–133, 138, 141). In fact, the correlation between physiological and morphological classes in the retina is sufficiently robust that reliable identification of class membership can be made based on morphology alone. This fact has proven to be of crucial importance for studies of neurogenesis (see sect. III*A*). Finally, while these cell classes share certain central targets, they form parallel streams of afferent inputs that remain largely segregated at least to the level of primary visual cortex. This segregation suggests independence, but much of the data reviewed here suggest that competitive interactions between functional cell classes may well occur during development. Because much less is known about W-cells, and because data from W-cells comparable to those reviewed here for X- and Y-cells are not yet available, we concentrate on the X- and Y-cell pathways.

A. Retinal Ganglion Cell Morphology

Boycott and Wassle (6) described separate classes of retinal ganglion cells using Golgi methods. One class, the α-cells, was found to have the largest somata and axons of any retinal ganglion cells, and they have large dendritic fields. β-Cells, in contrast, have smaller somata than α-cells at given locations on the retina (i.e., locally, β-cells have smaller somata than α-cells, but peripherally located β-cells can be as large as centrally located α-cells), and they have the smallest dendritic fields of all retinal ganglion cells. The third class identified by Boycott and Wassle (6) was the γ-cells, which have since been shown to be a relatively heterogeneous group possibly reflecting separate correlations with the various functional subtypes of W-cells (e.g., Refs. 87, 130).

A large number of early studies suggested that the α- and β-cells corresponded with physiologically classified Y- and X-cells, respectively. The methods employed in those studies, however, could not completely resolve the issue (14, 32, 99, 156, 157). The subsequent development of methods with which cells are stained intracellularly with horseradish peroxidase (HRP) have permitted direct structure-function analyses of retinal ganglion cells. Briefly, this method involves the extracellular characterization of retinal ganglion cells as X or Y using micropipettes filled with HRP. After the cells are classified, they are impaled and HRP is injected iontophoretically. Subsequent histochemical reactions provide a detailed Golgi-like morphological view of the physiologically identified cells, thereby permitting direct comparisons of the structure and function of individual neurons. Experiments of this sort have largely confirmed the earlier results obtained using less direct methods (30, 133).

B. Anatomy of the Lateral Geniculate Nucleus

Before proceeding to a description of the features of retinogeniculate axon terminations in the LGN, a brief digression to describe the structure of the LGN itself is in order. The LGN of cats is a laminated structure. The most commonly used nomenclature divides the nucleus into two A laminae, A and A1, and four C laminae, C, C1, C2, and C3, with lamina A being farthest from the optic tract and lamina C3 nearest (59). Laminae A, C, and C2 are innervated by retinal ganglion cells lying in the contralateral retina, while laminae A1 and C1 are innervated by axons arising from the ipsilateral retina. Layer C3 does not receive direct input from either retina. In addition to these differences in ocular dominance, the various layers also differ cytologically (40, 55, 58, 71) and in terms of the relative balance of inputs from the several physiological classes of retinal ganglion cells (61, 93, 166).

As for the retina, most relay cells in the LGN can be readily classified as X-, Y-, or W-cells, no doubt because they receive specific connections from retinal ganglion cells of the same class (e.g., Refs. 7, 62). In the cat, laminae A and A1 contain a mix of roughly equal proportions of X- and Y-cells (e.g., Refs. 13, 31, 61, 166). Laminae C1 and C2, on the other hand, contain only W-cells (e.g., Refs. 15, 31, 131, 132, 142, 166, 167). Layer C has a mixture of all three cell classes, but a partial segregation is present. Layer C is itself composed of two sublaminae, a dorsal sublayer of relatively larger cells made up of predominantly Y-cells with a small number of X-cells, and a ventral sublayer of smaller W-cells (23, 53, 59, 93, 95, 166; for reviews, see Refs. 51, 107, 116). There is, therefore, a fairly sharp segregation between X- and Y-cells in the A laminae and the dorsal sublamina of layer C and W-cells in the ventral sublamina of layer C and laminae C1 and C2.

C. Morphology of Retinogeniculate Axon Arbors

Retinogeniculate X and Y axons in normal cats have a termination in one of the A layers, lamina A if from the contralateral retina or lamina A1 if from the ipsilateral retina (5, 138, 141). Y-cell axons projecting contralaterally also usually have smaller arbors in lamina C (4, 5, 138, 141). A few contralaterally projecting X-cell axons also have very small arbors in layer C (138).

In addition to the basic observations regarding the laminar targets of X- and Y-cell axons, there have been several studies correlating the morphology of single retinogeniculate axon arbors with their physiological classification as X or Y (4, 5, 138, 141). While the total sample from all these studies is only ~50 axons, certain morphological differences between the arbors of X- and Y-cells have been consistently observed. Relative to Y axon arbors, X-cell arbors in lamina A or A1 are about one-half as broad mediolaterally. They are also much smaller volumetrically, having arbors about one-quarter as large as the A laminae termination of Y-cells, and they have only about one-half as many terminal boutons. These differences are not present at all stages of development, however, but rather reflect the end points of several processes that are ongoing over perhaps the last two-thirds of gestation and the first several months of postnatal life.

In most respects, the data reviewed above for the retinogeniculate system of cats are in good agreement with comparable observations in closely related ferrets (110, 136, 150, 169). There are, however, several differences. First, in ferrets (and minks), the A laminae are subdivided into leaflets that largely segregate inputs conveyed by on- and off-center ganglion cells (77, 89, 110, 136). Second, in ferrets, retinal Y-cells comprise a much smaller proportion of the ipsilateral projection to lamina A1 than the contralateral projection to lamina A (110, 150). Finally, the retinogeniculate axonal arbors of Y-cells in ferrets are much more widespread than they are in cats, with their terminations frequently extending into interlaminar zones and even inappropriate (for their eye of origin) laminae (110).

III. RETINOGENICULATE DEVELOPMENT

A. *Development of Retinal Ganglion Cells*

The establishment of structure-function relationships for retinal ganglion cells and their axonal arbors in the LGN has provided a significant new tool for studying the visual system and its development. For example, experiments using [^{3}H]thymidine labeling to study neurogenesis in the retina can provide information about the developmental histories of the first neural elements of the functionally distinct input streams.

Studies that have used [^{3}H]thymidine to study retinal neurogenesis have shown that the various morphological classes of ganglion cells are produced in broad overlapping waves (153, 154) superimposed on the central-to-peripheral developmental gradient (113, 153); that is, while cells in central retina undergo their final mitosis before those in peripheral retina, differences also exist within any patch of retina in the rates at which the various cell types become postmitotic. In general, with respect to β- and α-cells, the smaller β-cells tend to have earlier birthdates than α-cells, with their waves of development offset by ~4 days. This difference in the onset of neurogenesis of α- and β-cells is also reflected by fiber order in the optic tract in cats (151) and ferrets (152). In cats, and a range of other species, the oldest fibers (i.e., the first to enter the tract) lie deepest in the tract, while those that enter later lie nearer the pia (147). In cats, the older fibers are of medium caliber (β) while the larger axons of the α-cells lie nearer the pia (54, 102, 148). This relationship of functional axon type to relative position in the optic tract has been directly demonstrated by electrophysiological recording in the optic tract in adult cats (86). In addition, Sur et al. (138) injected retinogeniculate axons with HRP after they had been physiologically classified as X or Y. The parent trunks of X-cell axons were consistently located dorsal to the parent trunks of Y-cell axons which occupied positions closer to the pia. We cannot assume from these data alone that the X-cell pathway is functioning earlier in development than the Y-cell pathway, although this may be true. We can assume, however, that X-cell axons arising from β-cells in the retina probably have access to target tissue in the dorsal LGN earlier than do Y-cell axons arising from the retinal α-cells. If so, this temporal precedence would presumably confer some advantage on the earlier arriving X-cell axons over the later arriving Y-cell axons [e.g., see Meyer (91)].

B. *Development of Retinal Projections in the Lateral Geniculate Nucleus*

Considerably less information exists concerning the development of the arbors of X- and Y-cell axons in the LGN than for the more peripheral loci discussed thus far. Although a number of excellent studies have investigated the process of segregation of the afferents from the two eyes into eye-specific bands, our knowledge of the normal development of functionally characterized X- and Y-cell axons is limited by the absence of crucial bits of data. For example, in their elegant in vitro experiments in fetal cat tissue, Sretavan and Shatz (127) filled axons terminating in the LGN by making bulk injections of HRP in the optic tract. These methods have proven quite successful in extending our understanding of eye-specific segregation, but they do not permit axons filled in this manner to be identified as X or Y. Hence, these data cannot address the issue of possible differences in the prenatal developmental histories of X- and Y-cell axons. A similar lack of information exists for the first several weeks of postnatal life as well. Again, for a variety of technical and biological reasons [e.g., cloudiness of the ocular media (3, 24, 144)], it is not possible to characterize axons as X or Y early in postnatal life (18, 25, 26, 96). Thus the developmental histories of these axon classes can only be determined from the point when physiological classification is first possible. To date, the earliest successful experiments combining physiological classification with intracellular labeling have been performed in 3- to 5-wk-old kittens (26, 28, 143). The strategy we have adopted to over-

come these limitations is to perform a variety of manipulations on the developing visual system and then compare the morphologies of identified axons from such experimental animals with data from normal adults. Our review focuses on these experimental data. We contend that the development of the retinogeniculate system is controlled in large part by competitive interactions between sets of retinal afferents. These include *1*) competition between axons from the two eyes which contributes to the process of laminar segregation and *2*) competition between axons from the same eye which shapes the development of axonal arbors within their normal lamina of termination. We focus on X and Y axons and propose that these two classes of fibers have different developmental strategies, different sensitivities to a range of manipulations, and play different roles in the various kinds of pattern formations occurring during development.

IV. INTEROCULAR COMPETITION

A. Description of Ocular Segregation

In normal adult cats, the retinal projections from the two eyes form alternating eye-specific bands within the LGN corresponding to the cellular laminae (e.g., Refs. 47, 56). This is not always the case, however. At about embryonic day 35 (E35; gestation in cats is 65 days), the injection of an anatomic tracer into one eye labels the LGN rather uniformly, suggesting that the afferents from the two eyes are extensively overlapped (113). Such overlap could have arisen for one of two reasons, or a combination of the two. First, individual axons from one eye could encroach upon regions of the LGN where they would not be found to terminate in normally reared adult cats (4, 5, 139, 141). For example, contralaterally projecting axons might be found to terminate not only in the inner one-third of the nucleus (i.e., eventual lamina A), but in the middle one-third (i.e., eventual lamina A1) as well. Alternatively, there could be a substantial population of retinogeniculate axons with axons completely confined to inappropriate regions of the LGN. For example, ipsilaterally projecting axons might avoid the middle one-third of the nucleus (i.e., eventual lamina A1, their normal target) and elaborate arbors only in the inner one-third of the nucleus (i.e., eventual lamina A), normally the target of afferents from the contralateral retina. These scenarios lead to quite different pictures of the process by which eye-specific domains come to be established in the LGN during normal development. If some or all axons have arbors that involve both appropriate and inappropriate parts of the nucleus, the formation of eye-specific territories would presumably be the consequence of arbor retraction where the inappropriately located portion of the arbor is selectively eliminated. This developmental strategy operates in a number of other systems [e.g., neuromuscular junction (100)] and at other levels in the visual system (e.g., Ref. 66) and is, therefore, not unlikely. On the other hand, if many cells had axons that targeted only inappropriate zones in the LGN, their deaths might produce the eye-specific layers. This possibility is consistent with the huge wave of retinal ganglion cell death (168) and axon elimination in the optic nerve (163), much of which is temporally coextensive with the formation of eye-specific laminae during fetal development. In either event, however, it seems reasonable to postulate a role for binocular competitive interactions in the development of the segregation of retinogeniculate axons from the two eyes.

B. Elimination of Ongoing Binocular Interactions Postnatally

1. Early studies

The most straightforward way to study the role of competition between afferents from the two eyes in retinogeniculate development is to remove one eye, and thus one set of afferents. Guillery (49) demonstrated that afferents from the remaining eye are present in geniculate regions denervated by early postnatal monocular enucleation. In these experiments, Guillery (49) employed degeneration techniques in which the remaining eye was subsequently removed and its degenerating axons in the LGN were stained. Only lamina A, ipsilateral to the late-enucleated eye, was studied in these experiments because the methods employed made it problematic to distinguish between degeneration of axonal arbors as opposed to axons of passage. For example, degeneration products in lamina A1, contralateral to an enucleated eye, would be detectable simply because axons with arbors in lamina A must traverse it. Subsequent experiments using autoradiographic labeling of retinogeniculate afferents by intravitreal injections of [^{3}H]proline avoided such interpretive problems and showed that "sprouting" was present in both A laminae (57). Moreover, by the time the latter paper was published, it was clear that the phenomenon in question did involve sprouting, since it had been shown that axons from the two eyes were segregated at birth (103; see also Ref. 97). Thus the result could not be attributed to either a retention of translaminar exuberance existing at the time of enucleation or to the survival of mistargeted axons. Later experiments employed bulk injections of HRP in the optic tract to provide Golgi-like filling of individual retinogeniculate axons (104, 106). Results from these experiments showed unambiguously that single axons did indeed sprout into geniculate regions denervated by the monocular enucleation in addition to their normal targets. Data from all of these experiments showed that ongoing binocular interactions in early postnatal life are necessary for the maintenance of the segregation of retinogeniculate afferents already virtually completed by birth (see also Refs. 113, 114, 127).

2. Are all retinal axons equally capable of sprouting?

With the demonstration that individual axons have expanded terminations after early monocular enucle-

ation, the question remained as to whether all classes of retinogeniculate afferents contributed to the expansion. Results from Hickey's experiments (57) suggested that W-cell axons might sprout after early enucleation. The pattern of label in the C laminae appeared to be different in cats enucleated early compared with normal adult cats or cats enucleated as adults, suggesting some translaminar growth might have occurred. The normal absence of clearly defined interlaminar zones, however, rendered this observation equivocal. Because X and Y axons both terminate freely in the A laminae, and because workers employing bulk-filling methods were not able to distinguish X and Y axons based on their morphology (83), the question of whether X and Y axons might respond differently to early postnatal monocular enucleation remained. The introduction of intracellular HRP methods and their application to retinogeniculate fibers, however, permitted an investigation of whether X and Y axons sprout with equal propensity under these conditions. By the time these experiments were initiated, these two classes of axons had already been shown to have different postnatal developmental histories (143) and different sensitivities to monocular lid suture (140), suggesting that they might indeed react differently to monocular enucleation.

3. *Intracellular studies of early postnatal monocular enucleation*

In cats monocularly enucleated on the day of birth (P0), retinogeniculate axons were filled intracellularly with HRP after the cats were at least 1 yr of age (45). It is important to reemphasize at this point that ocular segregation is all but complete at birth (e.g., Ref. 114). The basic finding was that not a single X axon had expanded into denervated geniculate territory, while most of the Y axons had. Although the total sample was small (8 X, 15 Y axons), as is always the case with this sort of study, this result was robust. Moreover, a similar difference between 9 X and 12 Y axons was seen in a companion study that combined lid suture of the remaining eye with P0 monocular enucleation (44). It seems reasonable to conclude, therefore, that, at least during postnatal life, Y but not X axons require ongoing binocular interactions for their arbors in the LGN to remain confined to laminae appropriate to their eye of origin. Again, it is important to emphasize that the aberrant projections that are seen after early enucleation are the manifestation of growth and are not due to a retention of a normally transient exuberant projection existing at the time of enucleation (113, 127).

4. *Why should retinogeniculate X and Y axons differ in their capacity to sprout into denervated geniculate regions after P0 monocular enucleation?*

The fact that Y but not X axons sprout after P0 monocular enucleation reflects a fundamental difference between X and Y axons that might exist for one or more of several reasons. Perhaps Y axons sprout, while X axons do not, because they enjoy some kind of advantage in the process of innervating denervated LGN layers (e.g., greater light-evoked activity or the presence of a receptive substrate such as translaminar dendrites on cells in the denervated layers). Alternatively, as mentioned earlier, the initiation of Y axon development lags somewhat behind that of X axons. Perhaps Y axons can sprout after P0 enucleation because they are in the midst of a growth phase through which X axons have already passed. That is, perhaps Y axons sprout simply because they are less mature than X axons. Finally, X axons may simply be incapable of sprouting.

C. *Are Y Axons at a Competitive Advantage in Denervated Laminae?*

It is possible that Y axons are placed at a competitive advantage with respect to X axons by P0 monocular enucleation, and because of this advantage can extend sprouts into denervated laminae while X axons cannot? Competition between afferents from one eye has been previously posited as an important mechanism controlling the postnatal maturation of X and Y axons (for reviews, see Refs. 43, 114, 137; and see sect. v). It has been suggested, for example, that monocular eyelid suture establishes a competitive imbalance between retinogeniculate X and Y axons from the deprived eye with the later growing Y axons being placed at a disadvantage (see sect. v). Whether the details of that hypothesis are true or not, deprived Y axons definitely fail to develop normally; their A laminae arbors are much smaller than normal, and in some cases even lost completely. If Y axons enjoy some sort of competitive advantage against X axons when novel geniculate territory is made available by enucleation, perhaps this advantage can be reversed or partially mitigated by suturing the lids of the remaining eye after P0 monocular enucleation. In cats reared under such conditions, however, Y axons were again found to sprout freely into adjacent denervated geniculate laminae, while X axons were again found to have arbors restricted to their appropriate target layer. Therefore, even though Y axons may have been placed at a competitive disadvantage by the imposition of eyelid suture, they still sprouted heavily into denervated territory; and while X axons may have been placed at a competitive advantage, they still did not.

Another "advantage" that Y axons might enjoy in the context provided by early postnatal monocular enucleation is the selective availability of a receptive substrate. Guillery (46) had reported much earlier that a substantial number of geniculate neurons have dendrites that cross laminar borders, and he later suggested (49) that these dendrites might provide a pathway along which sprouting axons could travel. Subsequently, in the initial report on intracellularly filled LGN cells, Friedlander et al. (27) described numerous

morphological differences between cells that had been physiologically classified as X or Y. One key difference was that the dendritic trees of Y-cells were found to freely cross interlaminar zones, whereas X-cells were found to be confined to a single layer. This, together with the more recent observation that the portions of these cells' dendritic trees located in the "wrong" layer may well receive direct retinal innervation from the wrong eye (105), could offer Y axons an avenue for expansion that is unavailable to X axons. More recently, however, Humphrey and Weller (67) have reported that many of the intracellularly filled LGN X-cells in their sample have dendrites that cross laminar borders. They suggested that this difference between their data and those of Friedlander et al. (27) was due to the fact that the somata of the X-cells in the earlier sample tended to be found in the middle of geniculate layers, whereas many of the X-cells in their more recent sample had somata near laminar borders. In that view, whether a cell has dendrites crossing laminar borders becomes a correlate of the relative location of a cell's soma within the thickness of a layer and not of cell class. Apparently, therefore, the dendrites of many Y- and X-cells cross laminar borders, and this morphological feature, while it still might provide the pathway along which Y axons expand, cannot account for why X axons do not sprout into adjacent denervated layers.

D. Do Y Axons Sprout Because They Develop Later Than X Axons?

1. Prenatal monocular enucleation

As mentioned earlier, the onset of the development of the Y pathway lags somewhat behind that of the X pathway (153, 154). Therefore, it is possible that Y axons sprout after P0 enucleation and X axons do not because they are at different stages of a commonly shared developmental program. For example, Y axons could be in the midst of a rapid arbor elaboration phase [see Schneider et al. (112)] through which the X axons have already passed. The most obvious way to test this possibility is to perform the enucleations even earlier in development to determine if X axons can then form sprouts into normally inappropriate regions of the LGN. To accomplish this, monocular enucleations have been performed on fetuses on embryonic day 44 (E44; gestation in cats is 65 days). These fetuses were then returned to the womb for the last 3 wk of prenatal development. They were born normally and were prepared for intracellular experiments when they were at least 6 mo of age (41).

2. Development of the lateral geniculate nucleus after prenatal monocular enucleation

The development of geniculate lamination is markedly affected by the removal of one set of afferents this early in life (8, 42, 121, 159). The LGN, after E44 enucleation, consists of only two layers, a dorsal layer composed of medium and large cells and a ventral layer composed of small cells. We (42) have argued previously based on measurements of geniculate cell sizes and the pattern of termination of single retinogeniculate axons that the dorsal layer is a composite of the A laminae and the dorsal "magnocellular" sublamina of layer C (23, 53, 59, 95; for reviews, see Refs. 51, 107), whereas the ventral layer is a composite of the ventral "parvocellular" sublamina of layer C (see references above) and the remaining C laminae. Not surprisingly, then, all of the X and Y axonal arbors recovered from E44 enucleated cats are confined to the dorsal layer of the bilaminar LGN. Because the normal pattern of lamination is absent in these cats, and because all of the X and Y arbors are restricted to the dorsal lamina, a determination of whether or not retinogeniculate arbors are abnormally expanded must be made on grounds other than obvious translaminar growth. Nevertheless, X and Y arbors in the E44 enucleated cats differed dramatically, and the nature of the difference suggested that X axons were relatively unaffected by monocular enucleation even at this earlier age, while Y axons were again profoundly affected.

3. Intracellular studies after monocular enucleation on embryonic day 44

All of the X axons recovered from E44 enucleated cats appear essentially normal in terms of their size, shape, and apparent location within the nucleus (41). So, for example, X axons from the contralateral retina had normally proportioned cylindrical arbors located in the outermost part of the dorsal layer of the LGN, a region which would have been occupied by lamina A had development proceeded normally. Similarly, X axons from the ipsilateral retina terminated in a middle portion of the dorsal lamina of the LGN, a zone where lamina A1 would presumably have developed normally. Therefore, performing the monocular enucleation 3 wk earlier (at E44 rather than P0) did not result in abnormally expanded X axonal arbors. On the other hand, all of the Y axonal arbors recovered from the E44 enucleated cats were abnormal in either size, the location of their terminal arbor, or both. The majority (7 of 9) had arbors that spanned the entire dorsal layer of the LGN whether they arose from the ipsilateral or contralateral retina. Thus they were both abnormally tall and present in regions of the nucleus that would normally be innervated by the removed eye. Whereas the absence of the normal pattern of lamination makes interpretation somewhat more difficult than was the case with the P0 enucleated cats, these data clearly demonstrate that X axons are not abnormally large even when ongoing binocular interactions are interrupted as early as E44, 3 wk earlier than the P0 experiments.

4. Can X axons sprout?

Is it still possible that X and Y axons share a common developmental program that operates at a differ-

ent pace? What would be the status of X axons if monocular enucleation was performed even earlier in development? Data from a single cat that underwent monocular enucleation on E36 suggest that whereas some X axon arbors are indeed aberrant, there are none with arbors spanning abnormally large dorsoventral portions of the LGN (109). Moreover, Sretavan and Shatz (128) have performed in vitro bulk-filling experiments on E59 fetuses after E23 monocular enucleation, and those data can be partially interpreted in the present context. Somewhat surprisingly, they found that, at E59, none of the axons in the LGNs of E23 enucleated cats was abnormally large. Rather, axons from the remaining eye formed two tiers, one in the middle and one in the outer one-third of the nucleus (i.e., presumably where laminae A1 and A would have developed). Thus one tier in each nucleus was composed of appropriately located axonal arbors (i.e., middle one-third in the ipsilateral LGN and outer one-third in the contralateral LGN), while one tier in each nucleus contained inappropriately located arbors. Because physiological classification is not possible in these fetal in vitro experiments, it is not known whether these tiers reflect some sort of functional segregation (e.g., X vs. Y or on vs. off; cf. Ref. 42). However, because none of the arbors is abnormally large, these results demonstrate clearly that X axons do not sprout (or retain dorsoventral exuberance) even when ongoing binocular interactions are eliminated very near the beginning of retinal neurogenesis (153, 154). It appears, therefore, that retinogeniculate X and Y axons differ fundamentally in their reliance on ongoing binocular interactions during the development of their terminal arbors. Y axons seem to require interactions with afferents from the opposite eye to become and remain appropriately restricted (at least from E36 on). Moreover, these interactions are at least partially dependent on physiological activity, since some Y axons sprout when impulses from both eyes are blocked postnatally with tetrodotoxin (TTX; Ref. 139). X axons, on the other hand, develop normal-sized arbors even when binocular interactions have not been permitted (i.e., axons have not yet reached the optic chiasm at E23; Ref. 163).

It seems possible that the wide-ranging termination patterns of Y axons in ferrets might also be due to a major imbalance between inputs from the contralateral and ipsilateral eyes; that is, the relatively impoverished ipsilateral Y-cell projection (110, 150) could approximate monocular enucleation. The contralaterally projecting Y axons would then extend into lamina A1 because of the relative absence of ipsilaterally projecting Y axons. Consistent with this notion, the sole ipsilaterally projecting Y axon recovered from ferrets has a terminal field completely restricted to lamina A1, while six of the seven contralaterally projecting Y axons have clear terminations in lamina A1 (110).

E. Other Effects of Early Monocular Enucleation

A few Y axons from the E44 enucleated cats exhibited an abnormality that was not detected in any of the Y axons recovered from P0 enucleated cats. These two axons had arbors that seemed to be completely confined to inappropriate regions of the dorsal layer; that is, if ipsilaterally projecting, the axon's arbor was located in the outer portion of the nucleus where lamina A would have formed normally, and if contralaterally projecting, the axon's arbor was located in the center of the dorsal lamina where lamina A1 would have developed. Comparable abnormalities are also present when monocular enucleation is performed on E36 (109). In this cat, however, not only are Y axon arbors "mislocated," but some of the X axons also have aberrantly located arbors (109). Again, we should stress that these aberrant X arbors are not abnormally tall, but rather their relatively normal-sized arbors are located in what appear to be inappropriate zones in the LGN.

F. Role of Interocular Competition in Eye-Specific Segregation

1. Elimination of mislocated side branches

A comparison of the results of monocular enucleation at these various developmental stages may bear on the issue raised earlier of whether the eye-specific segregation of retinal afferents is achieved by reductions in size of individual arbors, the elimination of inappropriately targeted arbors, or both. The existence, during normal fetal development, of axons with branches in regions of the LGN inappropriate for the eye of origin is without question (126, 127). These authors (126, 127) used in vitro HRP bulk injections to fill retinogeniculate axons in fetal LGNs of known embryonic ages. They showed that during the period of prenatal development when afferents from the two eyes are extensively intermixed within the LGN (E38-E54), single axons from one eye have side branches located in regions of the nucleus destined to become dominated by inputs from the opposite eye. These inappropriately located side branches are subsequently eliminated, while at the same time the appropriately located portion of the arbor becomes more elaborate. Moreover, the time course over which these inappropriately located side branches are eliminated corresponds temporally with the emergence of eye-specific segregation. It seems more than likely, therefore, that the segregation occurs at least in part as a consequence of side-branch elimination. It should be noted, however, that the inappropriately located side branches are, even when maximal, relatively sparse. This sparseness prompted Sretavan and Shatz (126) to conclude that the segregation of retinal afferents from the two eyes is probably not accomplished solely by side-branch elimination.

2. Cell death in the retina

The retinal ganglion cell population is also not static during prenatal development, so it seems possible

that cell death in the retina may play a role in ocular dominance segregation as well. Williams et al. (163) reported that perhaps five to six times as many retinal ganglion cells are born as exist in the mature visual system (10, 162, 164). The largest wave of axon elimination in the optic nerve occurs before the beginning of the process of segregation (163), and presumably relates to other factors (see Refs. 9, 19, 165). A large number of axons are eliminated postnatally (163), after ocular segregation is completed (70, 103, 113), and also must relate to other factors (e.g., Ref. 78). In addition, however, many axons are eliminated as eye-specific segregation transpires (163), and their deaths could well contribute to the process. Thus, if the hypothesis is true that inappropriately located arbors are present because of the survival of retinal ganglion cells that would have died under normal developmental circumstances, then both α- and β-cells in the retina are subject to this form of competitive elimination. Because aberrant X arbors are found after E36 enucleation but not after E44 enucleation, this form of interocular competition could well be linked to the developmental time courses of α- and β-ganglion cells, with the wave of cell death due to this process ending earlier for β- than for α-cells (see sect. IV*H*).

3. Dynamics of eye-specific segregation

It seems probable based on the available evidence that both cell death in the retina and side-branch elimination in the LGN are involved in the process of eye-specific segregation of retinogeniculate afferents. The massive overlap of projections from the two eyes evident at the time of the E44 enucleations, therefore, would reflect not only the presence of side branches that are subsequently eliminated but also completely mistargeted arbors that are also normally eliminated because of the deaths of their somata in the retina. Another effect of prenatal enucleation (at E42 or E51) is that the normal process of cell death is modified. The remaining eye of such cats retains ~15–20% more ganglion cells than it would under normal conditions (10, 74). The inappropriately located arbors seen in cats monocularly enucleated on E36 or E44 might, therefore, arise from surviving retinal ganglion cells that would normally have died. Presumably, arbors of this sort are not found after P0 monocular enucleation because the retinal ganglion cells are already dead by the time of the operation, or because it is too late in development to create conditions that permit their survival.

G. Is the Height of X Axons Intrinsically Determined?

X axons, after monocular enucleation at either E44 or P0, appear relatively normal in size and location. Furthermore, at least their size is normal after enucleation at E23 or E36. Hence, binocular interactions are not required at all for the normal development of that aspect of their morphology. Whereas some X axons are inappropriately located after E36 (and, in all probability, E23) enucleation, they are found only in appropriate regions or laminae after E44 or P0 enucleation. Therefore, at least from the point of maximal overlap of afferents from the two eyes in the LGN (i.e., about E44), X axons do not require ongoing binocular interactions to accurately place their arbors. Moreover, they accomplish the apparently correct placement of their arbors whether the pattern of lamination in the nucleus is relatively normal (P0) or not (E44). Thus the dorsoventral restriction of X axon arbors must be independent of any cues that might arise from the process of interlaminar space formation. Apparently, however, some activity-dependent mechanism is necessary for the development of restricted X axon arbors. Sretavan et al. (129) delivered TTX to fetuses in utero beginning on E42. When axons were bulk-filled in vitro at E57 or E58, no normally restricted axonal arbors were detected, so while interactions with afferents from the other eye are not required for X axon arbor restriction, physiological activity is necessary, suggesting that the relevant interaction might be with cells in the LGN that were also probably silenced by their intracerebral delivery of TTX (129).

The fact that X axons do not seem to require ongoing binocular interactions to restrict the height of their arbors should not be taken to imply that they never transiently involve areas ultimately taken over by axons from the opposite eye. Sretavan and Shatz (127) noted that, at E44, most retinogeniculate axons have side branches in areas destined to become dominated by axons from the opposite eye. Because X axons are probably the first to reach the geniculate anlage and outnumber Y axons by ~10 to 1 (see Refs. 107, 116, 135), it seems more than likely that many of the fibers with mislocated side branches at E44 are X axons. Therefore, the difference in the capacities of X and Y axons to develop expanded arbors after monocular enucleation on E36, E44, or P0 cannot be due simply to whether or not side branches exist in inappropriate areas. Rather, these two classes of axons differ in their capacity to stabilize and maintain the normally transient expanded innervation (114) of inappropriate geniculate regions. Therefore, developing X and Y axons must differ in terms of intrinsically directed maturational programs, sensitivity to modifications of extrinsic milieu, or both (see Ref. 165).

H. Interocular Interactions: Summary

We discussed three factors that contribute to the development and stabilization of X and Y retinogeniculate arbors. The overriding question we began with was what mechanisms are responsible for the development of the mature forms of these axon arbors. Thus far, we have concentrated on dorsoventral (i.e., normally, eye specific) restriction within the LGN. During development, axons from the two eyes come to have arbors restricted to appropriate eye-specific laminae in the LGN.

We suggest that this process is accomplished via the operation of two mechanisms involving binocular interactions. First, direct interactions between the arbors of Y axons arising from the two eyes seem to play a role in the elimination of transient side branches in inappropriate geniculate territory. Second, we propose that interocular interactions also contribute to the elimination of axons with arbors that are restricted to inappropriate parts of the LGN. Finally, we hypothesize that X axons, because of the tenacity with which they avoid geniculate territory destined to be innervated by afferents from the opposite eye, may possess a greater affinity for their appropriate target zones in the LGN than do Y axons.

V. INTRAOCULAR COMPETITION

In addition to interocular competitive interactions that contribute to the development of eye-specific segregation within the LGN, data exist that strongly suggest that intraocular competitive interactions between X and Y retinogeniculate axons contribute significantly to the elaboration of their terminal arbors within a given layer of the LGN. The first evidence in support of the existence of competitive interactions between developing X and Y retinogeniculate axons arose from experiments on the effects of monocular visual deprivation on structure-function relationships of LGN neurons. Monocular deprivation has a long history of use for studying interocular competition stemming from the seminal studies of Wiesel and Hubel (160, 161) comparing the effects of monocular and binocular lid suture. Certainly, it is not immediately obvious why this manipulation would also prove of value in studying intraocular competition. As mentioned earlier, Friedlander et al. (27) demonstrated morphological differences between cells in the LGN that had been classified as X or Y. These observations, together with earlier reports of the selective effects of visual deprivation on geniculate Y-cells (e.g., Ref. 119), prompted an intracellular study in cats raised with monocular lid suture to determine if deprivation altered the morphology of geniculate neurons. A number of abnormalities were observed, but the most significant for the present argument was that ~25% of the recovered sample of deprived neurons that had been classified as X had morphological features normally associated with Y-cells (29). Because geniculate neurons are classifiable as X or Y because they receive X or Y retinogeniculate innervation (e.g., Refs. 7, 62), the existence of these cells implied that neurons that would normally have been Y-cells were receiving inputs from retinal X-cells, possibly because they had been placed at a competitive advantage with respect to deprived retinal Y-cells. Further support for the possibility that retinogeniculate X axons could make errors in connectivity by innervating cells in the LGN with Y-like morphology had in fact already been presented by Friedlander et al. (27). In that study of normal structure-function relationships in the LGN, a small number of cells were recovered that were physiologically unclassifiable. Cells in the LGN with mixed physiological properties presumably exist because they receive innervation from both retinal X- and Y-cells (e.g., Ref. 29, 123). It seems feasible that "mixed" cells and deprived X-cells in the LGN might both reflect the failure of a normal developmental process to reach a normal conclusion (for a brief review, see Ref. 36). It has also been noted that in 4- to 5-wk-old kittens, some cells are found with many adultlike X-cell physiological properties but with adult Y-cell somatic and dendritic morphology (146). Although it is possible that these cells would eventually develop Y-cell physiology as their receptive field properties mature, it is also possible that they represent another example of retinogeniculate X inputs to cells destined to become part of the Y pathway. These observations, together with observations of the normal postnatal development of X and Y retinogeniculate axonal arbors (see sect. v*A*), eventually prompted an intracellular investigation of the effects of deprivation on developing retinogeniculate axons.

A. Intralaminar Postnatal Development of X and Y Retinogeniculate Axons

Early in postnatal life (i.e., at 3–4 wk of age), retinogeniculate axonal arbors are very immature. X and Y axons differ, however, in the nature of their immaturity in a way which indicates that they follow fundamentally different developmental strategies to accomplish the elaboration of their arbors. At this stage of development, X axon arbors are actually larger in horizontal extent than the arbors of X axons in normal adult cats (143). They achieve their adult size through a process of retraction, a common developmental strategy, and are adultlike by the end of the third postnatal month. Y axons are also fully mature by ~12 wk of age. At 3–4 wk of age, however, their A laminae arbors are much smaller than in the normal adult (28, 117, 143). Therefore, they achieve their adult form not through a process of retraction, but rather through simple expansion. It is important to note here that we do not mean to imply that retinogeniculate X and Y axons necessarily develop at different rates, only that they follow different strategies. The early exuberant X axons are no more mature than still-expanding Y arbors.

The complementary changes in the sizes of X and Y axons during this period of postnatal development could reflect independent processes. Alternatively, the existence of cells with mixed physiological properties in normal cats and the presence of X-cells (defined physiologically) with Y-cell morphology in the deprived laminae of monocularly lid sutured cats suggested that X and Y retinogeniculate axons might be engaging in competitive interactions. Some additional indirect support for this notion was provided by the observation that the C laminae terminations of Y axons appear adultlike in size much earlier in development than the lamina A arbors of the same fibers (28). The earlier expansion might be made possible by the relative absence of X axon termi-

nations in the C laminae (5, 138, 141). In this view, the later-expanding A laminae Y axons actually prune the X axon arbors as they expand. The mixed cells would then represent a subtle developmental error in which the normally exuberant X axons fail to withdraw all of their contacts with LGN cells, which would otherwise develop into Y-cells (see Ref. 36). The deprived X-cells with Y-like morphology in the monocularly lid sutured cats would reflect one aspect of the outcome of interactions between X and Y axons from the same eye in a situation where the competitive balance has been shifted heavily in favor of the earlier expanding X axons, preventing the Y axons from successfully displacing them.

B. Do X and Y Axons Compete Within Lateral Geniculate Nucleus Laminae?

1. Effects of monocular eyelid suture

The hypothesis that X and Y retinogeniculate axons might engage in competition during postnatal development has been tested more directly by studying the effects of monocular eyelid suture on their development. The results of these experiments showed that deprived X axons were larger than normal, as if they had retained the normally transient portions of their terminal arbors which are evident in young kittens (140). Deprived Y axon arbors in the A laminae, on the other hand, were, on average, much smaller than normal. Indeed, some deprived Y axons from the contralateral retina which would normally terminate in both layer A and the C laminae were found to have no lamina A arborization at all (140). Importantly, the C laminae arbors of deprived Y axons from the contralateral retina appear qualitatively normal. Because X axons project heavily to the A laminae (5, 138, 141), but only contribute very sparse inputs to the dorsal part of the C lamina, it seems possible that the arbors of deprived Y axons from the contralateral retina developed normally in layer C because they were not subjected to the same degree of competitive interactions with X axons. A comparable pattern of Y axonal arbor shrinkage is found with binocular eyelid suture (101).

2. Effects of treatment with tetrodotoxin

Data from cats treated postnatally with binocular retinal impulse blockade with TTX suggest that the intraocular competition between X and Y retinogeniculate axons during development is activity dependent. As with the deprived axons in cats with monocular eyelid suture (140), X axons in cats treated with TTX are broader than they would be normally, and Y axons are narrower. Consistent with these effects is the observation that a much larger than normal proportion of deprived geniculate neurons is found to have converging inputs from both X and Y retinal ganglion cells (1, 20).

3. Effects of postnatal monocular enucleation within lateral geniculate nucleus laminae

Other data that have been used to support the hypothesis that retinogeniculate X and Y axons compete during development have been taken from cats reared with one eye enucleated. As discussed in section IV*D*, Y axons from the remaining eye sprout heavily into nearby geniculate territory denervated by early postnatal monocular enucleation while X axons do not. Despite the fact that their arbors remain confined to appropriate laminae, however, X axon arbors from cats monocularly enucleated on P0 are abnormal. The X axon arbors in these cats are larger than normal again as if they had retained the normally transient exuberant portions of their arbors. We speculated that the Y axons found it "easier" to sprout into adjacent denervated territory than to displace the earlier expanding X axon arbors that were already ensconced there, and freed from the intrusion of what would normally be more aggressive Y axons, the X axon arbors retained their immature exuberance. Some confirmation for this interpretation was provided by subsequent experiments in which we combined early postnatal monocular enucleation with lid suture of the remaining eye. Again, as mentioned earlier, Y axons from the remaining eye sprouted into denervated geniculate territory, while X axons remained confined to their appropriate target layer. Moreover, as with monocular eyelid suture alone, the A laminae arbors of the Y axons were smaller than normal, presumably because they were subject to the competitive disadvantage conferred by lid suture in the normally innervated A laminae. As for the X axons from cats reared with monocular enucleation alone, X axons from the lid-sutured monocularly enucleated cats were abnormal, with arbors 25–30% larger than normal, again suggesting that they had been permitted to retain normally transient exuberant elements in their arbors.

4. Effects of strabismus

Recently, the study of developing X and Y retinogeniculate arbors has been extended by examining the effects of cats reared with a convergent strabismus surgically induced by transecting the lateral rectus muscle of one eye (38, 108). As with monocular eyelid suture, the development of X and Y retinogeniculate axons was affected by this perturbation. Somewhat more surprisingly, axons from both the deviated and nondeviated eyes were equally affected. We interpret the former result as providing additional support for the X/Y competition hypothesis; that is, the A laminae arbors of Y axons in the strabismic cats were smaller than normal, whereas the X axon arbors were larger than normal. Moreover, as for the deprived contralaterally projecting Y axons from monocularly lid-sutured cats, the C laminae terminations of Y axons in the strabismic cats appeared completely normal, possibly because any competitive interactions with X axons would be comparatively

minor due to the sparseness of the X inputs to lamina C. These observations, in sum, are consistent with the hypothesis that X and Y retinogeniculate axons from one eye engage in activity-dependent competitive interactions during postnatal development, presumably for trophic substances available in the geniculate neuropil.

C. *Some Factors Controlling Intralaminar Size of X and Y Arbors*

The data reviewed thus far demonstrate that the sizes of X and Y axonal arbors within the A laminae are not intrinsically determined. X axonal arbors are found to remain larger than normal under rearing conditions that stunt the growth of Y axons (e.g., monocular eyelid suture or strabismus), suggesting that the process by which X arbors normally become smaller as they mature involves competitive pruning by the later expanding Y arbors. On the other hand, although Y arbors can achieve and/or maintain inappropriate terminations when provided the opportunity to occupy portions of the LGN denervated by enucleation, their large sizes under these circumstances are in no way due to expansions within their normal target laminae. Thus the proposed intralaminar competitive interactions between X and Y axons operate under constraints that are intrinsically determined. For example, X axons are no larger after monocular enucleation combined with eyelid suture than after either of those manipulations alone, suggesting the existence of an upper limit of size that cannot be exceeded.

Clearly, the intralaminar growth of Y axons can be rather easily disrupted, but are there circumstances under which Y axon arbors can elaborate overly large arbors within their appropriate target layer? Neonatal visual cortex ablation has a selective and severe effect on the X pathway (124). Most β-cells in the retina die via transneuronal retrograde degeneration (72, 98), and their death can be confirmed electrophysiologically (145, 149). The LGN is severely shrunken in adult cats after neonatal ablation of visual cortex as a consequence of retrograde degeneration, but the geniculate laminae are discernible (see Ref. 124). Thus this manipulation permits an assessment of the postnatal development of Y axon arbor morphology within their normal target laminae that are largely devoid of X-cell inputs. Weber et al. (158) recorded and intracellularly injected retinogeniculate Y axons in adult cats that had undergone neonatal visual cortex ablation. Despite the near absence of an X pathway, all of the Y axons in their sample were similar in size to Y axons in normal cats (unpublished data from our laboratory confirm this result). Thus intralaminar Y arbor size is controlled independently of target size (i.e., the LGN is severely shrunken), and their normal intralaminar size may also be their maximum size.

We hypothesize, therefore, that the lateral extents of X and Y axonal arbors in the A laminae are determined by competition and afferent activity, respectively; that is, we propose that the mature widths of X axons are achieved via competitive pruning by the later expanding Y axons. Alternatively, Y axons require normal activity to achieve their mature widths. Thus Y axons fail to develop completely when deprived of patterned visual inputs by eyelid suture (140) or when their activity is blocked by TTX (139), and in these cases, X axon arbors are larger than normal. Finally, this requirement of Y axons for "normal" activity extends beyond simple neighborhood relationships within one retina (see Refs. 84, 85, 90) because their development is disrupted by simply misaligning the visual axes (38). This result suggests that normal binocular experience is a necessary condition for Y axon development when both eyes are present. An experiment that suggests itself as a further test of this possibility would be to rear kittens with equal alternating monocular exposure since, with this manipulation, both eyes remain intact while binocular experience is prevented.

One implication of the hypothesis concerning possible intraocular competitive interactions between X and Y axons is that developing Y axons are more selective for particular postsynaptic cells than X axons. This, of course, implies that the LGN is not a tabula rasa, with individual relay cells acquiring their physiological identity based solely on the nature of their inputs. Rather, cells in the nucleus would, under normal developmental conditions, acquire and/or retain inputs from the class of retinal afferents appropriate for their extraretinally determined class membership. This is a moderately provocative hypothesis, but the issue of whether intrinsic or environmental determinants guide the commitment to a particular cell class is far from settled (see Ref. 11, 88). Perhaps the most direct way to study this issue is to eliminate retinal afferents before they reach the LGN, and then to investigate the morphological features of surviving neurons in the nucleus, but this experiment has not yet been performed in cats. Guillery et al. (52) did remove retinal afferents before they reached the LGN in ferrets, but their principal goal was to study the effects of this manipulation on the development of geniculate lamination. They did note, however, that relative differences in cell sizes developed normally in these animals; that is, cells in parts of the nucleus nearest the optic radiations, which would normally form the A laminae, were larger than those lying near the optic tract where the C laminae would form. They also noted that a size gradient existed such that cells became progressively smaller from medial to lateral in the nucleus, a trend found in the A laminae of normal ferrets (22) and cats (40). A similar result has been obtained in the tammar wallaby (82) and in macaque monkeys (R. Williams and P. Rakic, personal communication). While the sizes of somata in the A laminae are highly correlated with cell type (27, 67), it would be of great interest to know if other morphological features, such as dendritic arbor shape, develop normally as well. In any event, these data suggest that at least some aspects of morphological differentiation occur in the absence of retinal innervation. Thus relay cells in the cat LGN could well be specified

before retinal afferents ever enter the nucleus, leaving to the afferents the chore of selecting appropriate target sites. The fact that Y axons achieve their mature size and shape during postnatal development by simple expansion suggests that they may well demonstrate a greater selectivity in target selection than the X axons.

D. Binocular Effects of Strabismus

Unlike the effects of rearing cats with monocular eyelid suture, axons from both eyes are affected in strabismic cats (38, 108) even though both eyes are provided with reasonably normal monocular vision. This was certainly not the first demonstration of abnormalities associated with the normal eye of strabismic cats (e.g., Refs. 12, 40, 63, 122), but it raises anew the question of how manipulating the lateral rectus muscle of one eye could possibly affect the development of retinogeniculate axons from the other eye.

1. Binocular competition without advantage?

As previously noted, monocular eyelid suture, another unilateral perturbation, has substantial effects that are confined to inputs arising from the deprived eye. Because some of the effects of monocular deprivation are far more pronounced than would be predicted from a knowledge of binocular eyelid suture, it has been proposed that the effects of monocular deprivation are due largely to the imposition of a competitive imbalance between inputs from the two eyes (for review, see Ref. 120). Artificial strabismus also creates abnormalities in binocular interactions, but unlike with monocular lid suture, neither eye appears to enjoy a competitive advantage (40, 64). Thus Y axons from both eyes of strabismic cats are more or less equally disadvantaged by the deviation of one eye. Implicit in this argument is the presumption that the immature prebinocular nervous system does not recognize which eye is the source of the disruption. Perhaps the absence of normal patterns of correlated activity at the level of cortex initiates a retrograde cascade of effects extending transynaptically to the retinogeniculate junction.

2. Disruption of correlated activity along lines of projection

Alternatively, it is possible that the effects of strabismus are related to disruptions in normal patterns of correlated activity, but at the level of the LGN rather than cortex. As described in section IV, the elimination of ongoing binocular interactions by prenatal (41, 109) or early postnatal monocular enucleation (45) permits Y axons to sprout into nearby denervated geniculate territory. This observation suggests that during normal development Y axons are excluded from the wrong laminae by the presence of afferents from the other eye. This process of exclusion in turn suggests that the sets of Y afferents from the two eyes engage in some form of communication. Certainly one can imagine that such communication exists because Y axons don't normally sprout into laminae serving the other eye, and disabling the communication by administering TTX binocularly also results in some abnormal expansion on the part of Y axons (139). If Y afferents from the two eyes do communicate during development, perhaps the communication conveys more than simply ocularity. Under normal conditions, axons innervating adjacent laminae along a projection column (e.g., Refs. 2, 69, 111) would fire in a correlated fashion since their receptive fields would be homonymous. Perhaps such correlated activity is an important stimulus for normal development. If the visual axes are misaligned, the activity of axons innervating adjacent laminae would not be correlated, and without information about which set of axons arises from the deviated eye, the development of both sets is affected. Regardless of mechanism, however, these results demonstrate that retinogeniculate Y axon development is severely affected by disruptions in normal binocular vision.

3. Cues associated with misaligned visual axes

It is important to note, however, that the deleterious effects on both sets of afferents revealed by the experiments on esotropic cats cannot be due simply to misalignment of the visual axes per se. During development, normal binocular visual experience is required for the acquisition of normal eye alignment. Thus monocular eyelid suture and dark rearing both prevent the development of ocular alignment (e.g., Ref. 17, 73, 115), but neither results in aberrant development of retinogeniculate arbors from both eyes (see sect. V*E*). The bilateral effects of esotropia, therefore, must arise due to some other factor. One feature of stimulus disruption that esotropia does not share with monocular lid suture or dark rearing is the very active disturbance of vision (i.e., the diplopia). An esotropic cat is challenged to generate a cyclopian view of the world from diplopic inputs. Thus any effect of deprivation might be viewed as a relatively passive response to degraded or absent inputs, whereas the effects of esotropia more probably reflect the operation of a very active mechanism. Finally, these rearing paradigms might differ with respect to the quality of the extraocular proprioceptive signals available; that is, the quality of the proprioceptive signal available from a sectioned muscle no doubt differs dramatically from that arising from an unperturbed muscle and might in itself provide a powerful cue that a profound disruption in the binocular system exists. A number of experiments could be performed to assess these possibilities. In any event, the results from strabismic cats point out quite dramatically how exquisitely sensitive developing retinogeniculate axons are to deviations from normal experience.

E. Dark Rearing

As a reminder that nothing is ever so simple as one might wish, the results from dark-rearing experiments require discussion. Because eyelid suture had been found to have such a significant effect on retinogeniculate development, cats reared in the total absence of light have also been studied with the expectation that Y axons would be abnormal just as after patterned visual deprivation by lid suture. Surprisingly, both X and Y retinogeniculate axons appeared completely normal (37). As for the bilateral effects of strabismus, this was not the first demonstration that eyelid suture and dark rearing have different effects on aspects of morphological development. For example, eyelid suture beginning early in life has been consistently found to result in a failure of normal growth of cells in LGN laminae innervated by a deprived retina (21, 29, 33, 33–35, 39, 48, 50, 55, 58, 60, 65, 71, 76, 79, 81, 94, 118, 155, 160, 161). In dark-reared cats, on the other hand, the growth of geniculate neurons may occur at a somewhat slower pace, but full size is attained (71, 75). Certainly, deprivation via eyelid suture differs in several respects from that accomplished with dark rearing. Dark rearing completely eliminates visual stimulation, whereas lid suture merely prevents pattern vision while only moderately reducing the amount of light reaching the retina (16, 80). In fact, it is possible to plot the receptive fields of cortical neurons even when the eyelids are closed (125), and cats can make gross pattern discriminations through closed lids (80). In view of the differing effects of lid suture and dark rearing on the development of retinogeniculate X and Y axons, this difference in visual stimulation is evidently of great importance. Certainly, it belies Jampolsky's (68) suggestion that dark rearing totally inhibits development, whereas degraded or disorganized inputs permit the visual system to develop, albeit abnormally. Rather, our results suggest that some aspects of development can proceed normally in the dark but are profoundly disrupted if abnormal inputs are permitted.

VI. SUMMARY

The data reviewed here permit several general conclusions regarding the morphological development of X and Y retinogeniculate axons in cats. First, both interocular and intraocular competitive interactions shape development, and X and Y retinogeniculate afferents differ in their sensitivity to these interactions. Second, developmental disruptions can perturb the maturation of X and Y afferents in two distinctly different ways; retinal axons may fail to achieve or maintain appropriately located arbors with respect to the pattern found after normal ocular segregation, or the sizes of their arbors within their appropriate target laminae may be aberrant.

A. Location

The appropriate targeting of retinogeniculate projections onto the LGN can be disrupted in one of two ways. First, when normal interocular interactions are disrupted by monocular enucleation performed between E36 and the day of birth, many Y axonal arbors develop or fail to retract terminations within zones of the LGN normally destined to be dominated by inputs from the removed eye. Thus these Y axons have portions of their arbors in both appropriate and inappropriate regions of the nucleus. X axons with similar features are never found after monocular enucleation, even when the enucleation is performed as early as E23. It is proposed that X and Y axons differ fundamentally in this regard, presumably due to differing genetically prescribed constraints on their dorsoventral sizes. Second, axons with arbors that are apparently totally confined to inappropriate zones of the LGN are occasionally found after monocular enucleation. Y axons displaying this abnormality have been found after monocular enucleation performed on E44 and E36 (and, in all probability, E23), but not after enucleation on the day of birth. X axons with inappropriately located arbors have been found after monocular enucleation on E36 (and probably E23), but not after enucleation on E44 or P0. It is proposed that these aberrantly located arbors reflect the survival of retinal cells normally destined to die during development. The differing probabilities of finding Y or X axons with this abnormality after monocular enucleation performed at different stages of development may be due to different cell death schedules, perhaps related to the differences in their birthdates.

B. Intralaminar Size

Several manipulations, including monocular eyelid suture and strabismus, disrupt the normal intralaminar development of X and Y arbors. When this sort of abnormality is observed, it is always the case that the intralaminar arborizations of X axons are larger, and Y axons are smaller than they are in normal adult cats. Because X axons normally achieve their mature intralaminar size via a process of overgrowth and retraction whereas Y axons grow to their mature size without overgrowth and retraction, it is proposed that normally occurring intraocular competition between these axon classes has been impeded. Thus this sort of abnormality may be due to the stabilization of their immature sizes as a consequence of the impoverishment of the postnatal visual environment.

C. Roles of Activity and Light in Development

There can be no doubt that activity plays a significant role in the development of retinogeniculate axons. Both inter- and intralaminar development is disrupted when the sodium channel blocker TTX is present, either

pre- or postnatally. Moreover, data from dark-reared cats, in which the morphological development of retinogeniculate axons apparently proceeds normally, suggest that the pattern of correlated activity normally present in the retina is sufficient. However, the failure of deprived axons to develop normally when deprivation is accomplished by eyelid suture demonstrates that if light is present, patterned vision must be normal. Finally, data from cats reared with strabismus demonstrate that if patterned vision is available to both eyes, there is an additional requirement that the inputs from the two eyes must be correlated in some way for development to proceed normally. These final considerations have tantalizing implications for what one might expect to observe after a number of other rearing procedures for which no data exist. For example, what would be the effects of rearing cats with anisometropia, equal or unequal alternating monocular exposure, or with vision permitted through prisms? In any event, the results reviewed herein demonstrate that the development of retinogeniculate projections involves a sequence of events that is exquisitely sensitive to experience.

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