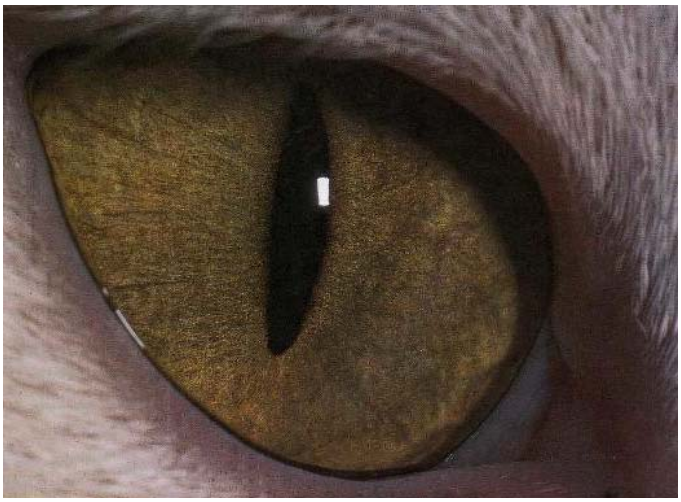
9. DEPRIVATION AND DEVELOPMENT



The slit shape of the pupil found in many nocturnal animals such as this cat presumably allows more effective light reduction than a circular pupil.

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Up to now we have been thinking of the brain as a fully formed, mature machine. We have been asking how it is connected, how the parts function in terms of everyday situations, and how they serve the interests of the animal. But that leaves untouched an entirely different and most important question: How did the machine get there in the first place?

The problem has two major components. Much of the brain's development has to go on in the mother's uterus, before the animal is born. A glance at the brain of a newborn human tells us that although it has fewer creases and is somewhat smaller than the adult brain, it is otherwise not very different. But a glance can hardly tell us the whole story, because the baby is certainly not born knowing the alphabet or able to play tennis or the harp. All these accomplishments take training, and by training, we surely mean the molding or modification of neuronal circuits by environmental influences. The ultimate form of the brain, then, is a result of both prenatal and postnatal development. First, it involves a maturation that takes care of itself, depends on intrinsic properties of the organism, and occurs before or after the time at which birth happens to occur; second, it involves postnatal maturation that depends on instruction, training, education, learning, and experience—all more or less synonymous terms.

Prenatal development is a gargantuan subject; I know little about it and certainly will not attempt to describe it in any detail here. One of the more interesting but baffling topics it deals with is the question of how the individual nerve fibers in a huge bundle find their proper destinations. For example, the eye, the geniculate, and the cortex are all formed independently of each other: as one of them matures, the axons that grow out must make many decisions. An optic-nerve fiber must grow across the retina to the optic disc, then along the optic nerve to the chiasm, deciding there whether to cross or not; it must then proceed to the lateral geniculate body on the side it has selected, go to the right layer or to the region that will become the right layer, go to just the right part of that layer so that the resulting topography becomes properly ordered, and finally it must branch and the

branches must go to the correct parts of the geniculate cells—cell body or dendrite. The same requirements apply to a fiber growing from the lateral geniculate body to area 17 or from area 17 to area 18. Although this general aspect ofneurodevelopment is today receiving intense study in many laboratories, we still do not know how fibers seek out their targets. It is hard even to guess the winner out of the several major possibilities, mechanical guidance, following chemical gradients, or homing in on some complementary molecule in a manner analogous to what happens in immune systems. Much present-day research seems to point to many mechanisms, not just to one.

This chapter deals mainly with the postnatal development of the mammalian visual system, in particular with the degree to which the system can be affected by the environment. In the first few stages of the cat and monkey visual path—the retina, geniculate, and perhaps the striate, or primary visual, cortex—an obvious question is whether any plasticity should be expected after birth. I will begin by describing a simple experiment. By about 1962 some of the main facts about the visual cortex of the adult cat were known: orientation selectivity had been discovered, simple and complex cells had been distinguished, and many cortical cells were known to be binocular and to show varying degrees of eye preference. We knew enough about the adult animal that we could ask direct questions aimed at learning whether the visual system was malleable. So Torsten Wiesel and I took a kitten a week old, when the eyes were just about to open, and sewed shut the lids of one eye. The procedure sounds harsh, but it was done under anesthesia and the kitten showed no signs of discomfort or distress when it woke up, back with its mother and littermates. After ten weeks we reopened the eye surgically, again under an anesthetic, and recorded from the kitten's cortex to learn whether the eye closure had had any effect on the eye or on the visual path.

Before I describe the results, I should explain that a long history of research in psychology and of observations in clinical neurology prompted this experiment. Psychologists had experimented extensively with visual deprivation in animals in the 1940s and 1950s, using behavioral methods to assess the effects. A typical experiment was to bring animals up from birth in complete darkness. When the animals were brought out into the light, they turned out to be blind or at least very defective visually. The blindness was to some extent reversible, but only slowly and not in most cases completely.

Paralleling these experiments were clinical observations on children born with cataracts. A cataract is a condition in which the lens of the eye becomes milky, transmitting light but no longer permitting an image to form on the retina. Cataracts in newborns, like those in adults, are treated by removing the lenses surgically and compensating by fitting the child with an artificial lens implant or with thick glasses. In that way, a perfectly focused retinal image can be restored. Although the operation is relatively easy, ophthalmologists have been loath to do it in very young infants or babies, mainly because any operation at a very early age carries more risk statistically, although the risk is small. When cataracts were removed, say at an age of eight years, and glasses fitted, the results were bitterly disappointing. Eyesight was not restored at all: the child was blind as ever, and profound deficits persisted even after months or years of attempts to learn to see. A child would, for example, continue to be unable to tell a circle from a triangle. With hopes thus raised and dashed, the child was generally worse off, not better. We can contrast this with clinical experience in adults: a man of seventy-five develops cataracts and gradually

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loses sight in both eyes. After three years of blindness the cataracts are removed, glasses fitted, and vision is completely restored. The vision can even be better than it was before the cataracts developed, because all lenses yellow with age, and their removal results in a sky of marvelous blue seen otherwise only by children and young adults.

It would seem that visual deprivation in children has adverse effects of a sort that do not occur at all in adults. Psychologists commonly and quite reasonably attributed the results of their experiments, as well as the clinical results, to a failure of the child to learn to see or, presumably the equivalent, to a failure of connections to develop for want of some kind of training experience.

Amblyopia is a partial or complete loss of eyesight that is not caused by abnormalities in the eye. When we sewed closed a cat's or monkey's eye, our aim was to produce an amblyopia and then to try to learn where the abnormality had arisen in the visual path. The results of the kitten experiment amazed us. All too often, an experiment gives wishy-washy results, too good to dismiss completely but too indecisive to let us conclude anything useful. This experiment was an exception; the results were clear and dramatic. When we opened the lids of the kitten's eye, the eye itself seemed perfectly normal: the pupil even contracted normally when we shined a light into it. Recordings from the cortex, however, were anything but normal. Although we found many cells with perfectly normal responses to oriented lines and movement, we also found that instead of about half of the cells preferring one eye and half preferring the other, none of the twenty-five cells we recorded could be influenced from the eye that had been closed. (Five of the cells could not be influenced from either eye, something that we see rarely if ever in normal cats.) Compare this with a normal cat, in which about 15 percent of cells are monocular, with about 7 percent responding to the left eye and 7 percent to the right. The ocular-dominance histograms for the cat, shown in the top graph on the facing **page**, allowed us to see the difference at a glance. Clearly something had gone wrong, with a vengeance.

We soon repeated the experiment in more kittens and in baby monkeys. In kittens, a larger series soon showed that if an eye is closed at birth, on the average only 15 percent of cells prefer the eye that was closed, instead of about 50 percent. The same results were found in monkeys (see the bottom histogram). Of the few cells that did respond through the eye that had been closed, many seemed abnormal; they fired sluggishly, fatigued easily, and lacked the normal precise orientation tuning.

A result like this raises many questions. Where in the visual path was the abnormality? In the eye? The cortex? Could the cat see with the eye that had been closed, despite the cortical abnormality? Was it light or form deprivation that produced the abnormality? Was the age at which we closed the eye important? Was the abnormality a result of disuse or of something else? To get answers to such questions took a long time, but we can state the results in a few words.

The obvious way to determine the site of the abnormality was to record at lower levels, starting, say, in the eye or the geniculate. The results were unequivocal: both the eye and the geniculate had plenty of cells whose responses were virtually normal. Cells in the geniculate layers that received input from the eye that had been closed had the usual center-surround receptive fields; they responded well to a small spot and poorly to diffuse light. The only hint of abnormality was a slight sluggishness in the responses of these cells, compared with the responses of cells in the layers fed by the normal eye.

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Given this relative normality, we were amazed when we first saw the Nisslstained lateral geniculate under the microscope. It was so abnormal that a microscope was hardly needed. The cat's geniculate has a somewhat more simple organization than the monkey's; it consists mainly of two large-cell layers, which are on top rather than on the bottom, as in the monkey. The upper layer receives input from the contralateral eye, the lower from the ipsilateral. Beneath these layers is a rather poorly defined small-cell layer with several subdivisions, which I will ignore here. On each side, the large-cell layer receiving input from the closed eye was pale and clearly thinner than its companion, which looked robust and perfectly normal. The cells in the abnormal layers were not only pale but were shriveled to about two-thirds their normal cross-sectional area. This result for a right-eye closure is shown in the photographs on the page 6. Similar results were found in the macaque monkey k for a right-eye closure, as shown in the photograph below. We thus faced a paradox that took us a few years to explain: a lateral geniculate whose cells seemed relatively normal physiologically but were manifestly pathological histologically. Our original question was in any case answered, since cortical cells, although virtually unresponsive to the closed eye, were evidently receiving a substantial and, on the face of it, practically normal geniculate input. This seemed to exonerate both the eye and the geniculate as primary sites of the damage and placed the main abnormality in the cortex. When we looked at the cortex histologically, we saw absolutely nothing to suggest any abnormality. As we will see, the cortex does show anatomical defects, but they do not show up with these staining methods.

We next asked what it was about the eye closures that produced the abnormality. Closing the eye reduces the light reaching the retina by a factor of about ten to fifty; of course, it also prevents any images from reaching the retina. Could it be simply the reduction in light that was causing the trouble? To help decide, we inserted in one eye of a newborn kitten an opalescent contact lens made of a plastic with the consistency of a ping pong ball. In some animals we instead surgically sewed over one eye a thin, translucent, opalescent membrane, in effect, an extra eyelid called the nictitating membrane that cats possess and we don't. The plastic or the membrane reduced the light by about one-half but prevented the formation of any focused images. The results were the same: an abnormal cortical physiology; an abnormal geniculate histology. Evidently it was the form deprivation rather than light deprivation that was doing the damage.

In a few kittens we tested vision before recording by putting an opaque black contact lens over the eye that had not been closed and then observing how the animal made out. The animals were clearly blind in the eye that had been deprived: they would walk confidently over to the edge of a low table, go past the edge, and fall to a mattress placed on the floor. On the floor they would walk into table legs. These are things no normal, self-respecting cat ever does. Similar tests with the eye that had not been closed showed that vision was entirely normal.

Next we did a protracted study in both cats and monkeys to learn whether the age at which the closures were done and the duration of the closures were important. It soon became clear that age of onset of deprivation was critical. An adult cat deprived of vision in one eye for over a year developed no blindness in that eye, no loss of responses in the cortex, and no geniculate pathology.

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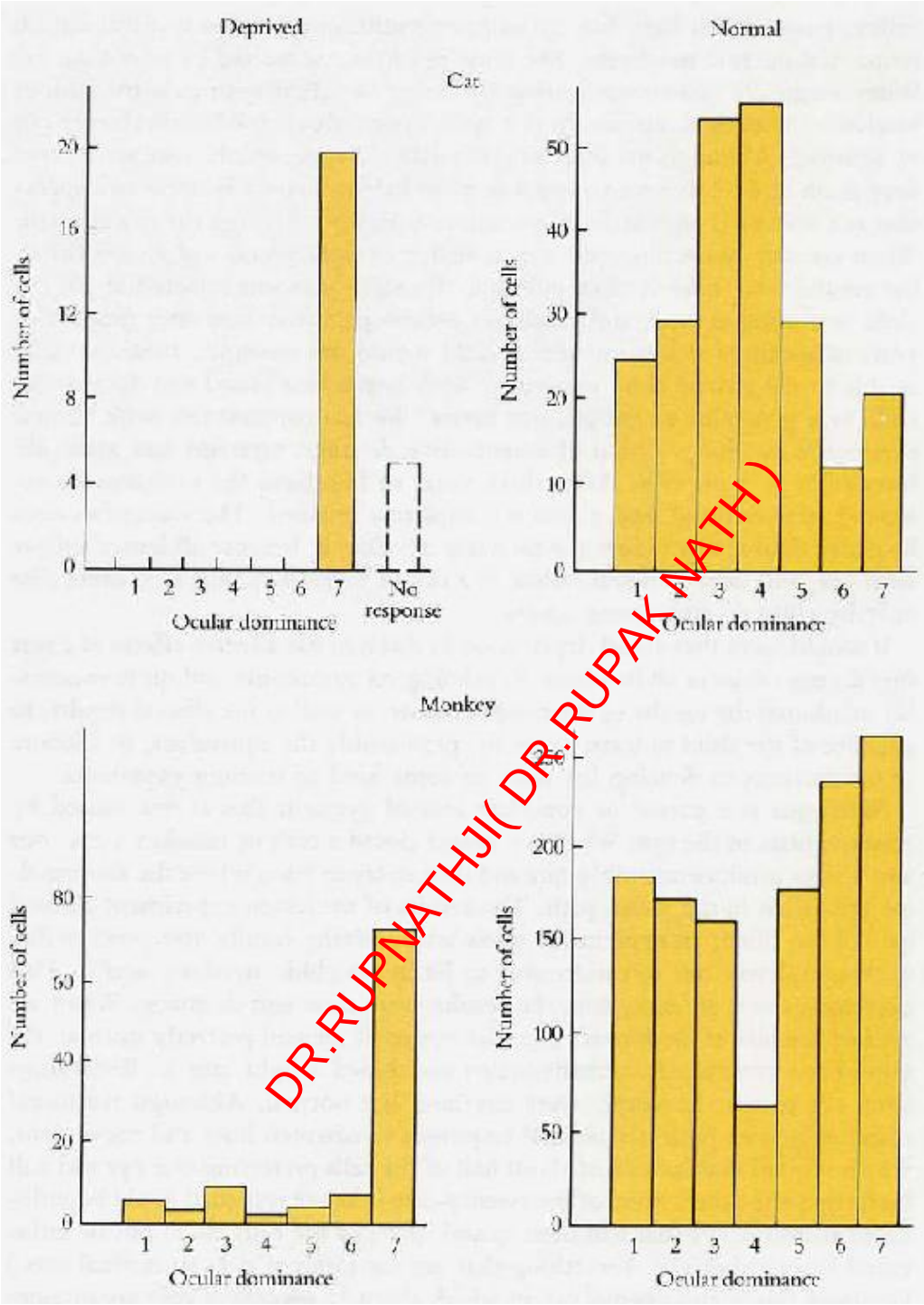

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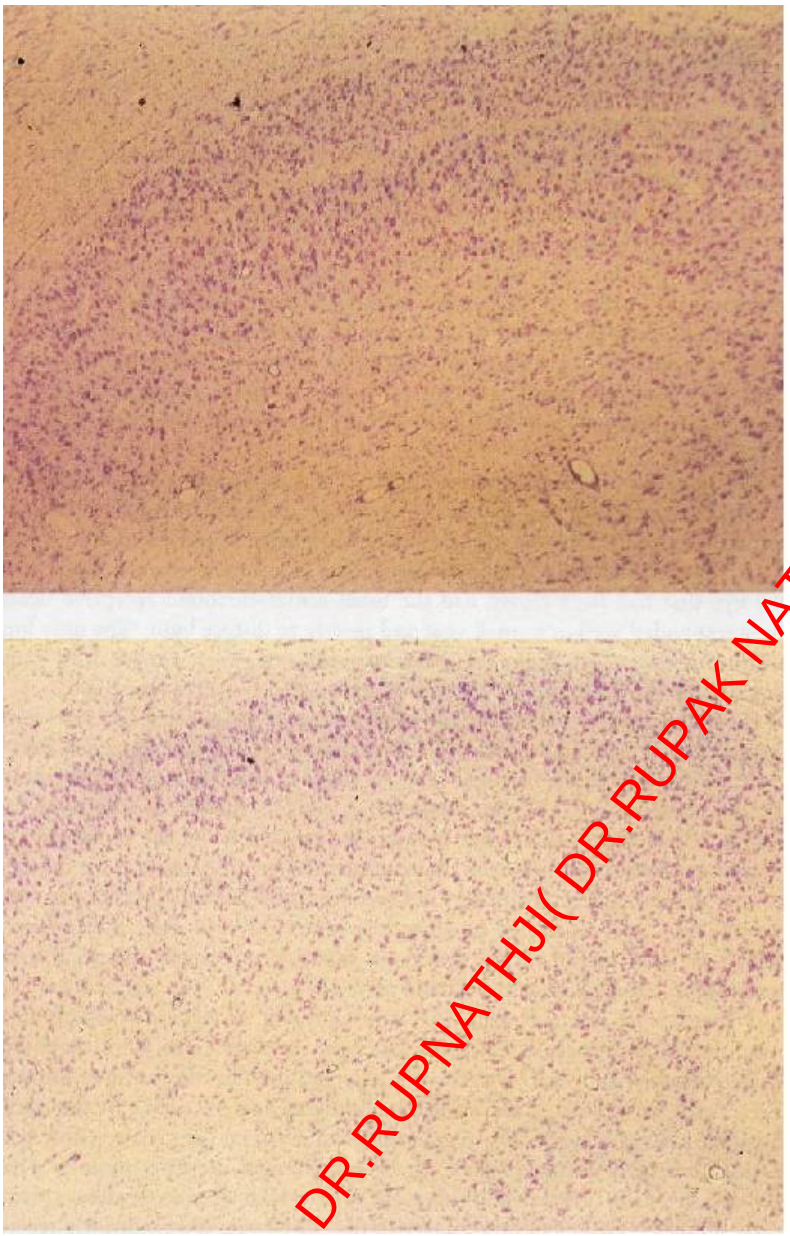
A kitten (top histograms) was visually de- prived after having its right eye closed at about ten days, the time at which the eyes normally open. The duration of closure was two-and-a-half months. In this experiment we recorded from only twenty-five cells. (In subsequent experiments we were able to record more cells, and we found a small percentage that were influenced from the eye that had been closed.) The results were very similar for a baby monkey (bottom histograms). It had its right eye closed at two weeks, and the eye remained closed for eighteen months. We subsequently found that the result is the same if the eye is closed for only a few weeks.



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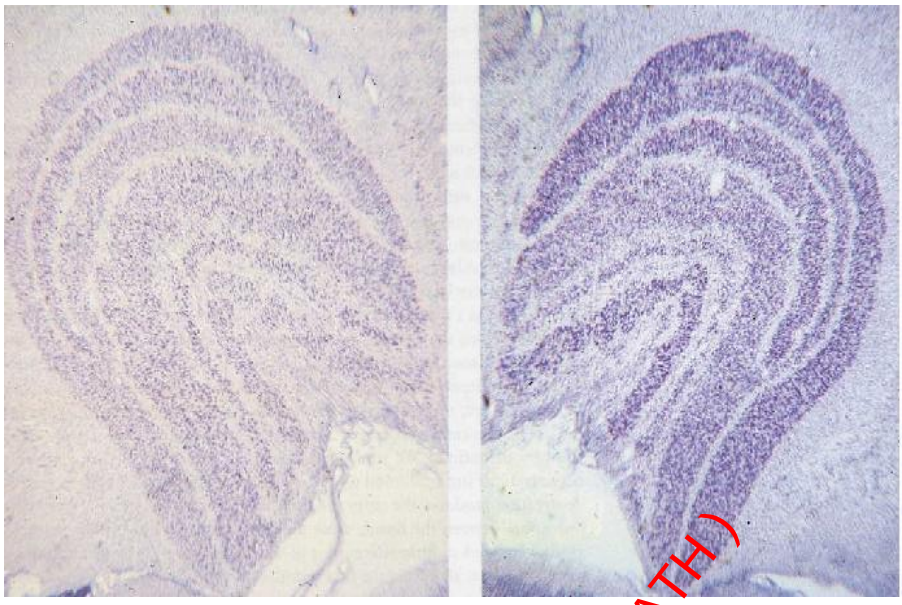
The lateral geniculate bodies of a kitten show obvious abnormalities when the right eye has been closed at ten days for thrce-and-a-half months. The two main layers can be seen in the top half of the photographs. Top; In the left geniculate the upper layer (contralateral to the closed, right eye) is shrivelled and pale staining. Bottom: In the right geniculate the lower of the two layers (ipsilateral) is abnormal. The two layers together are about 1 millimeter thick. The ocular-dominance histogram is shown at the top of the previous page.



Abnormal layers appear in the left and right lateral geniculate bodies (seen in cross section) of a monkey whose right eye was closed at age two weeks for eighteen months. On both sides, the layers receiving input from the eye that was closed (the right eye) are paler: layers 1, 4, and 6 on the left; layers 2, 3, and 5 on the right, numbered from below. The cells in the affected layers are smaller, but this cannot be seen at such low power. The width of the entire structure is about 5 millimeters.

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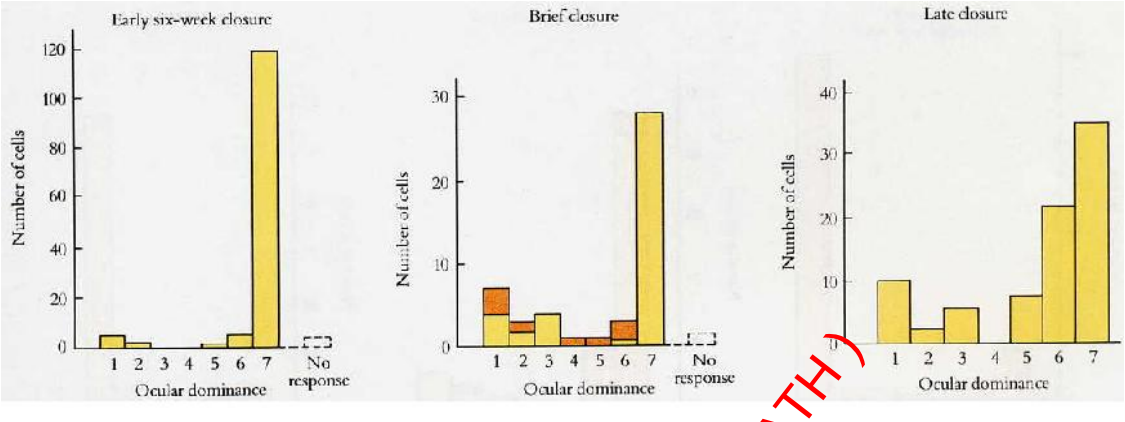
(The first cat we deprived, the mother of our first litter of kittens, was an adult by definition.) We concluded after many experiments that somewhere between birth and adulthood there must be a period of plasticity during which deprivation produces the cortical deficit. For the cat, this *critical period* turned out to be between the fourth week and the fourth month. Not surprisingly, closing an eye had little effect prior to the fourth week, because a cat uses its vision hardly at all during the first month of its life: the eyes open only around the tenth day, and for the next few weeks the kittens are behind the sofa with their mother. The susceptibility to deprivation comes on quickly and reaches a maximum in the first few weeks of the critical period. During that time, even a few days of closure result in a palpably distorted ocular-dominance histogram. Over the ensuing four months or so, the duration of closure required to give obvious effects increases steadily; in other words, the susceptibility to deprivation tapers off.

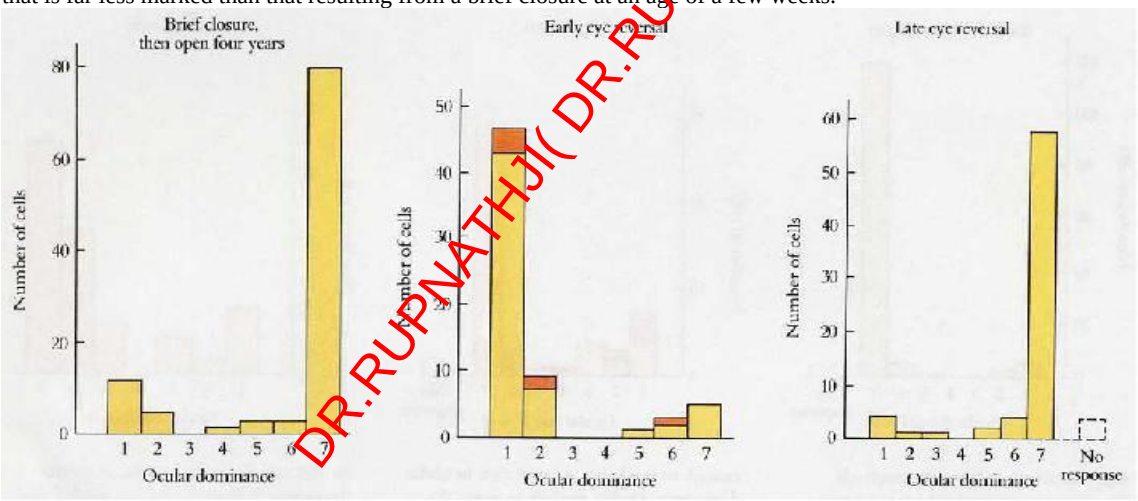
The histograms summarizing some of the results in monkeys can be seen in the three graphs on page 5. The left graph shows the severe effects of a six-week closure done at five days; almost no cells could be driven from the eye that was closed. A much briefer early closure (middle graph) also gave severe effects, but clearly not quite as severe as the longer closure. At four months the susceptibility begins to wane, so much so that even a closure of five years' duration, as shown in the righthand graph, although giving pronounced effects, is no match for the results of the earlier closure.

In these studies of the time course of the sensitive period, cats and monkeys gave very similar results. In the monkey, the sensitive period began earlier, at birth rather than at four weeks, and lasted longer, gradually tapering off over the first year instead of at around four months. It reached its peak in the first two weeks of life, during which even a

few days of closure was enough to give a marked shift in ocular dominance. Closing the eye of an adult monkey produced no ill effects, regardless of the duration of closure. In one adult monkey, we closed an eye for four years, with no blindness, cortical deficit, or geniculate-cell shrinkage.



Left: The left eye is almost completely dominant in a monkey whose right eye was sutured closed at an age of five days, for six weeks. *Middle*: A closure of only a few days in a monkey a few weeks old is enough to produce a marked shift in ocular dominance. Darker shading indicates the number of abnormal cells. *Right*: If the closure of the monkey's eye is delayed until age four months, even a very long closure (in this case five years) results in an eye-dominance shift that is far less marked than that resulting from a brief closure at an age of a few weeks.



1: One eye was closed at birth for nine days in this monkey and then opened. The recordings were done four years later, during which time the animal had had much testing of its vision. Even that long a period with both eyes open produced little recovery in the physiology. *2*: The right eye in this macaque monkey was closed at birth. At five and a half weeks the right eyelids were opened and the left closed. When at six months the recording was made from the right hemisphere, most of the cells strongly favored the right, originally closed eye. *3*: In this macaque monkey the right eye was closed at seven days, for one year, at which time the right eye was opened and the left was closed. After another year, the left eye was opened, and both remained open. When finally the recording was made at three and a half years, most cells favored the eye that was originally open. Evidently one year is too late to do a reverse suture.

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RECOVERY

We next asked whether any recovery in physiology in a monkey could be obtained by opening the eye that had been closed. The answer was that after a week or more of eye closure, little or no physiological recovery ever occurred if the closed eye was simply opened and nothing else done. Even a few years later, the cortex was about as abnormal as it would have been at the time of reopening the eye, as shown in the left graph on the previous page. If at the time of reopening, the other, originally open eye was closed, in a procedure called eye reversal, recovery did occur but only if the reversal was done when the monkey was still in the critical period, as shown in the middle and right-hand graphs above for early and late eye reversal. After the critical period, even an eye reversal followed by several years with the second eye closed failed to bring about anything more than slight recovery in the anatomy or physiology.

The monkey's ability to see did not necessarily closely parallel the cortical physiology. Without reversal, the originally closed eye never recovered its sight. With reversal, sight did return and often approached normal levels, but this was so even in late reversals, in which the physiology remained very abnormal in the originally closed eye. We still do not understand this disparity between the lack of substantial physiological or anatomical recovery and what in some cases seemed to be considerable restoration of vision. Perhaps the two sets of tests are measuring different things. We tested the acuity of vision by measuring the ability to discriminate such things as the smallest detectable gap in a line or circle. But testing this type of acuity may yield an incomplete measure of visual function. It seems hard to believe that such florid physiological and anatomical deficits in function and structure would be reflected behaviorally by nothing more than the minor fall in acuity we measured.

THE NATURE OF THE DEFECT

The results I have been describing made it clear that a lack of images on the retina early in life led to profound long-lasting defects in cortical function. These results nevertheless left open two major questions concerning the nature of the underlying process. The first of these was a "nature versus nurture" question: Were we depriving our animals of an experience that they needed in order to build the right connections, or were we destroying or disrupting connections that were already present, prewired and functional at the time the animal was born? The dark-rearing experiments done in the decades prior to our work had practically all been interpreted in the context of learning—or failure to learn. The cerebral cortex, where most people thought (and still think) that memory and mental activity resides, was looked upon in roughly the same way as the 1-megabyte memory board for which we pay so much when we buy our computers: these contain many elements and connections, but no information, until we put it there. In short, people regarded the cortex as a *tabula rasa*.

One obvious way to decide between these alternatives is to address the question head on and simply record from a newborn cat or monkey. If learning is necessary for the wiring up to occur, then we should fail to find any of the rich specificity that we see in adult animals.

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The Japanese macaque monkey, Macaca fiiscata, the largest of all macaques, lives on the ground and in trees in northern Japan. It is protected by its thick grey-brown coat.

A lack of specificity would nevertheless not decide the issue, because we could then ascribe the lack of connections either to immaturity—still-incomplete genetically programmed wiring—or to lack of experience. On the other hand, finding such specificity would argue against a learning mechanism. We did not expect the experiments with kittens to be easy, and they weren't. Kittens arc visually very immature at birth and make no use at all of their eyes before about the tenth day, when the eyes open. At that time, even the media of the eye, the transparent substances between the cornea and the retina, are far from clear, so that it is impossible to get a clear image on the retina. The immature visual cortex indeed responded sluggishly and somewhat unpredictably and was on the whole a far cry from a normal adult visual cortex; nevertheless we found many clearly orientation-specific cells. The more days that elapsed between birth and recording, the more the cells behaved like adult cells: perhaps because the media were clearer and the animal more robust but perhaps because learning had occurred. Interpretations differed from one set of observers to another.

The most convincing evidence came from newborn monkeys. The day after it is born, a macaque monkey is visually remarkably mature: unlike a newborn cat or human, it looks, follows objects, and takes a keen interest in its surroundings. Consistent with this behavior, the cells in the neonate monkey's primary visual cortex seemed about as sharply orientation-tuned as in the adult. The cells even showed precise, orderly sequences of orientation shifts (see the graph on page 12). We did see differences between newborn and adult animals, but the system of receptive-field orientation, the hallmark of striate cortical function, seemed to be well organized.

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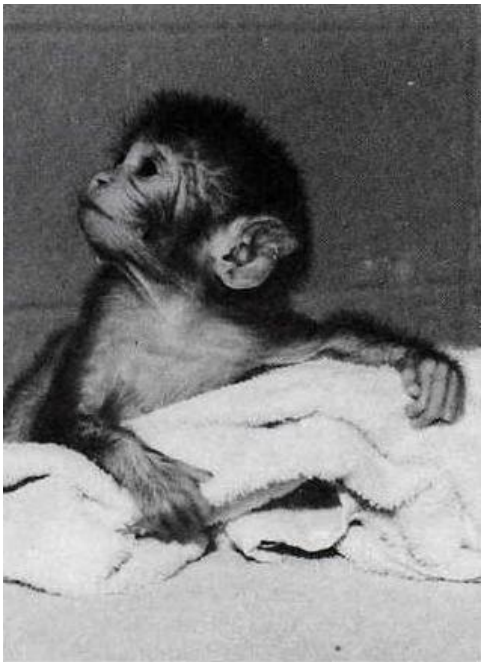

In a newborn macaque monkey, the cortical cells seem about as sharply tuned for orientation as in adult monkeys, and the sequences are about as orderly.

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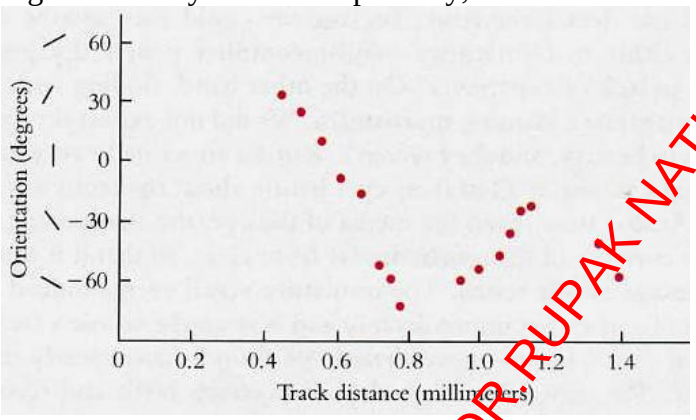
Compared with that of the newborn cat or human, the newborn macaque monkey's visual system may be mature, but it certainly differs anatomically from the visual system of the adult monkey. A Nissl-stained section of cortex looks different: the layers are thinner and the cells packed closer. As Simon LeVay first observed, even the total area of the striate cortex expands by about 30 percent between birth and adulthood. If we stain the cortex by the Golgi method or examine it under an electron microscope, the differences are even more obvious: cells typically have a sparser dendritic tree and fewer synapses. Given these differences, we would be surprised if the cortex at birth behaved exactly as it does in an adult. On the other hand, dendrites and synapses are still sparser and fewer a month before birth. The nature-nurture question is whether postnatal development depends on experience or goes on even after birth according to a built-in program. We still are not sure of the answer, but from the relative normality of responses at birth, we can conclude that the unresponsiveness of cortical cells after deprivation was mainly due to a deterioration of connections that had been present at birth, not to a failure to form because of lack of experience. The second major question had to do with the cause of this deterioration. At first glance, the answer seemed almost obvious. We supposed that the deterioration came about through disuse, just as leg muscles atrophy if the knee or ankle is immobilized in a cast. The geniculate-cell shrinkage was presumably closely related to *postsynaptic atrophy*, the cell shrinkage seen in the lateral geniculates of adult animals or humans after an eye is removed. It turned out that these assumptions were wrong. The assumptions had seemed so self-evident that I'm not sure we ever would have thought of designing an experiment to test them. We were forced to change our minds only because we did what seemed to us at the time an unnecessary experiment, for reasons that I forget.

We sutured closed both eyes, first in a newborn cat and later in a newborn

monkey. If the cortical unresponsiveness in the path from one eye arose from disuse, sewing up both eyes should give double the defect: we should find virtually no cells that responded to the left or to the right eye. To our great surprise, the result was anything but unresponsive cells: we found a cortex in which fully half the cells responded normally, one quarter responded abnormally, and one quarter did not respond at all. We had to conclude that you cannot predict the fate of a cortical cell when an eye is closed unless you are told whether the other eye has been closed too. Close one eye, and the cell is almost certain to lose its connections from that eye; close both, and the chances are good that the control will be preserved. Evidently we were dealing not with disuse, but with some kind of eye competition. It was as if a cell began by having two sets ofsynaptic inputs, one from each eye, and with one pathway not used, the other took over, preempting the territory of the first pathway, as shown in the drawing below.



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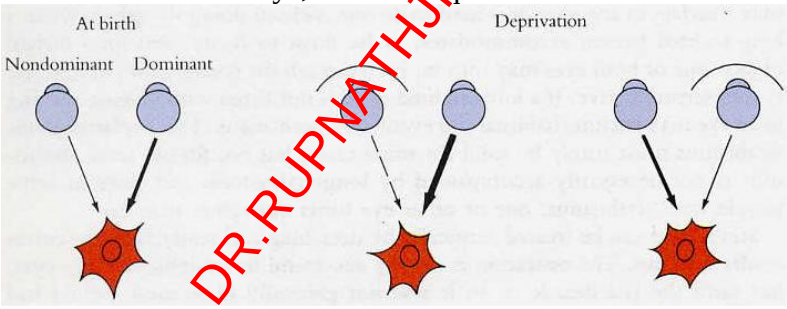

We suppose a cortical cell receives input from two sources, one from each eye, and that covering one eye has the effect of weakening the connections from that eye and strengthening the connections from the other one.

Such reasoning, we thought, could hardly apply to the geniculate shrinkage because geniculate cells are monocular, with no obvious opportunities for competition. For the time being we could not explain the cell shrinkage in the layers corresponding to the closed eye. With binocular closure, the shrinkage of geniculate cells seemed less conspicuous, but it was hard to be sure because we had no normal layers to use as a standard of comparison. Our understanding of this whole problem did not move ahead until we began to use some of the new methods of experimental anatomy.

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STRABISMUS

The commonest cause of amblyopia in humans is *strabismus*, or *squint*, terms that signify nonparallel eyes—cross-eye or wall-eye. (The term *squint* as technically used is synonymous with strabismus and has nothing to do with squinching up the eyes in bright light.) The cause of strabismus is unknown, and indeed it probably has more than one cause. In some cases, strabismus comes on shortly after birth, during the first few months when in humans the eyes would just be starting to fixate and follow objects. The lack of straightness could be the result of an abnormality in the eye muscles, or it could be caused by a derangement in the circuits in the brainstem that subserve eye movements.
In some children, strabismus seems to be the result of long-sightedness. To focus properly at a distance, the lens in a long-sighted eye has to become as globular as the lens of a normal eye becomes when it focuses on a near object. To round up the lens for close work means contracting the ciliary muscle inside the eye, which is called *accommodation*. When a normal person accommodates to focus on something close, the eyes automatically also turn in, or converge. The figure on this page shows the two processes. The circuits in the brainstem for accommodation and convergence are probably related and may overlap; in any case, it is hard to do one without doing the other. When a long-sighted person accommodates, as he must to focus even on a distant object, one or both eyes may turn in, even though the convergence in this case is counterproductive. If a long-sighted child is not fitted with glasses, turning in an eye may become habitual and eventually permanent.

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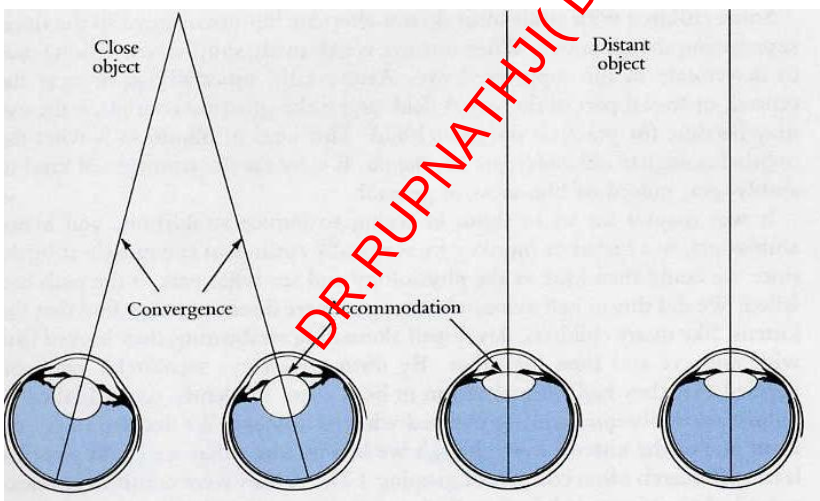

When we look at a near object two things happen: the lens rounds up because ciliary muscles contract, and the eyes turn in.

This explanation for strabismus must surely be valid for some cases, but not for all, since strabismus is not necessarily accompanied by long-sightedness and since in some people with strabismus, one or other eye turns out rather than in.
Strabismus can be treated surgically by detaching and reattaching the extraocular muscles. The operation is usually successful in straightening the eyes, but until the last decade or so it was not generally done until a child had reached the age of four to ten, for

the same reason that cataract removal was delayed—the slight increase in risk. Strabismus that arises in an adult, say from an injury to a nerve or eye muscle, is of course accompanied by double vision. To see what that is like, you need only press (gently) on one eye from below and one side. Double vision can be most annoying and incapacitating, and if no better solution is available, a patch may have to be put over one eye, as in the Hathaway shirt man. The double vision otherwise persists as long as the strabismus is uncorrected. In a child with strabismus, however, the double vision rarely persists; instead, either alternation or suppression of vision in one eye occurs. When a child alternates, he fixes (directs his gaze) first with one eye, while the nonfixating eye turns in or out, and then fixes with the other while the first eye is diverted. (Alternating strabismus is very common, and once you know about the condition, you can easily recognize it.) The eyes take turns fixating, perhaps every second or so, and while one eye is looking, the other seems not to see. At any instant, with one eye straight and the other deviating, vision in the deviated eye is said to be *suppressed*. Suppression is familiar to anyone who has trained himself to look through a monocular microscope, sight a gun, or do any other strictly one-eye task, with the other eye open. The scene simply disappears for the suppressed eye. A child who alternates is always suppressing one or other eye, but if we test vision separately in each eye, we generally find both eyes to be normal. Some children with strabismus do not alternate but use one eye all the time, suppressing the other eye. When one eye is habitually suppressed, vision tends to deteriorate in the suppressed eye. Acuity falls, especially in or near the central, or foveal part of the visual field, and if the situation continues, the eye may become for practical purposes blind. This kind of blindness is what the ophthalmologists call *amblyopia ex anopsia*. It is by far the commonest kind of amblyopia, indeed of blindness in general. It was natural for us to think of trying to induce strabismus, and hence amblyopia, in a kitten or monkey by surgically cutting an eye muscle at birth, since we could then look at the physiology and see what part of the path had failed. We did this in half a dozen kittens and were discouraged to find that the kittens, like many children, developed alternating strabismus; they looked first with one eye and then the other. By testing each eye separately, we soon verified that they had normal vision in both eyes. Evidently we had failed to induce an amblyopia, and we debated what to do next. We decided to record from one of the kittens, even though we had no idea what we could possibly learn. (Research often consists of groping.) The results were completely unexpected. As we recorded from cell after cell, we soon realized that something strange had happened to the brain: each cell responded completely normally, but only through one eye. As the electrode advanced through the cortex, cell after cell would respond from the left eye, then suddenly the sequence would be broken and the other eye would take over. Unlike what we had seen after eye closure, neither eye seemed to have suffered relative to the other eye in terms of its overall hegemony.

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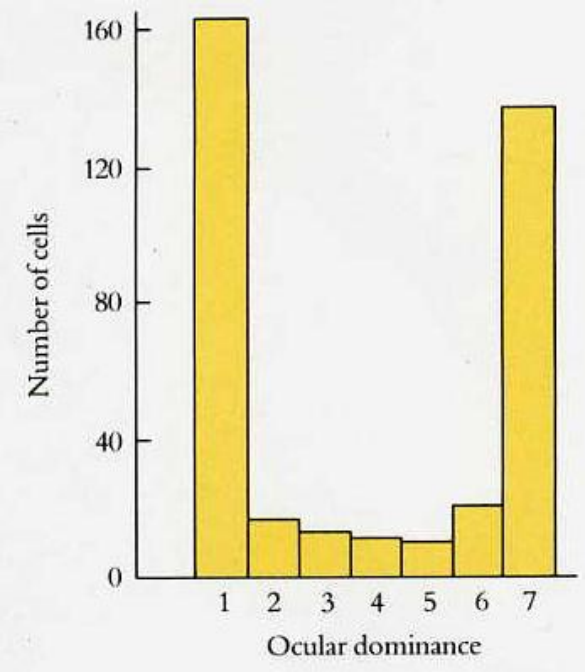

After we cut one eye muscle in a kitten at birth and then recorded after three months, the great majority of cells were monocular, falling into groups 1 and 7.

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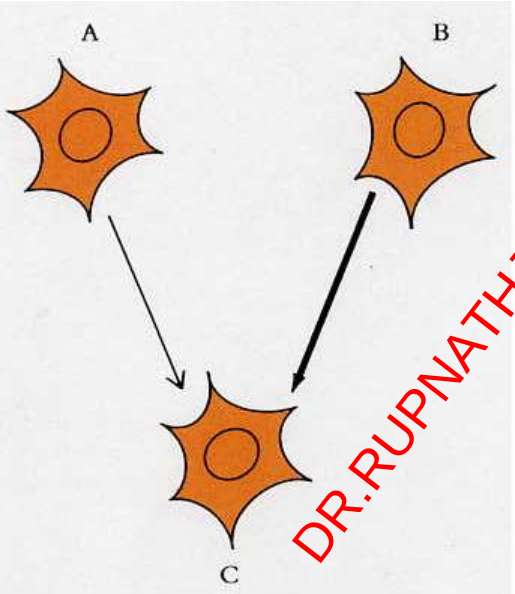
Binocular cells occasionally appeared near the points of transition, but in the kittens, the proportion of binocular cells in the population was about 20 percent instead of the normal 85 percent, as shown in the graph on this page.

We wondered whether most of the originally binocular cells had simply died or become unresponsive, leaving behind only monocular cells. This seemed very unlikely because as the electrode advanced, the cortex of these animals yielded the usual richness of responding cells: it did not seem at all like a cortex depleted of four-fifths of its cells. In a normal cat, in a typical penetration parallel to the surface in the upper layers, we see about ten to fifteen cells in a row—all dominated by the same eye, all obviously belonging to the same ocular-dominance column—of which two or three may be monocular. In the strabismic animals we likewise saw ten to fifteen cells all dominated by one eye, but now all but two to three were monocular. Each cell had apparently come to be dominated completely or almost completely by the eye it had originally merely preferred.

To appreciate the surprising quality of this result you have to remember that we had not really interfered with the total amount of visual stimulus reaching either retina. Because we had no reason to think that we had injured either eye, we assumed, correctly as it turned out, that the overall traffic of impulses in the two optic nerves must have been normal.

How, then, could the strabismus have produced such a radical change in cortical function? To answer this we need to consider how the two eyes normally act together. What the strabismus had changed was the relationship between the stimuli to the two eyes. When we look at a scene, the images in the two retinas from any point in the scene normally fall on locations that are the same distance and in the same direction from the two foveas—they fall on corresponding points. If a binocular cell in the cortex happens to

be activated when an image falls on the left retina—if the cell's receptive field is crossed by a dark-light contour whose orientation is exactly right for the cell—then that cell will also be excited by the image on the right retina, for three reasons: (1) the images fall on the same parts of the two retinas, (2) a binocular cell (unless it is specialized for depth) has its receptive fields in exactly the same parts of the two retinas, and (3) the orientation preferences of binocular cells are always the same in the two eyes. If the eyes are not parallel, reason 1 obviously no longer applies: with the images no longer in concordance, if at a given moment a cell happens to be told to fire by one eye, whether the other eye will also be telling the cell to fire is a matter of chance. This, as far as a single cell is concerned, would seem to be the only thing that changes in strabismus. Somehow, in a young kitten, the perpetuation over weeks or months of this state of affairs, in which the signals from the two eyes are no longer concordant, causes the weaker of the two sets of connections to the cell to weaken even further and often for practical purposes to disappear. Thus we have an example of ill effects coming not as a result of removing or withholding a stimulus, but merely as a result of disrupting the normal time relationships between two sets of stimuli—a subtle insult indeed, considering the gravity of the consequences.



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Cell C receives inputs from A, a left-eye cell, and B, a right-eye cell. The Hebb synapse model says that if cell C fires after cell A fires, the sequence of events will tend to strengthen the A-to-C synapse.

In these experiments, monkeys gave the same results as kittens; it therefore seems likely that strabismus leads to the same consequences in humans. Clinically, in someone with a long-standing alternating strabismus, even if the strabismus is repaired, the person does not usually regain the ability to see depth. The surgeon can bring the two eyes into alignment only to the nearest few degrees. Perhaps the failure to recover is due to the loss of the person's ability to make up the residual deficit, to fuse the two images perfectly by bringing the eyes into alignment to the nearest few minutes of arc. Surgically repairing

the strabismus aligns the eyes well enough so that in a normal person the neural mechanisms would be sufficient to take care of the remaining few degrees of fine adjustment, but in a strabismic person these are the very mechanisms, including binocular cells in the cortex, that have been disrupted. To get recovery would presumably require protracted reestablishment of perfect alignment in the two eyes, something that requires normal muscle alignment plus an alignment depending on binocular vision.

This model for explaining a cell's shift in ocular dominance is strongly reminiscent of a synaptic-level model for explaining associative learning. Known as the Hebb synapse model, after psychologist Donald Hebb of McGill University, its essential idea is that a synapse between two neurons, A and C, will become more effective the more often an incoming signal in nerve A is followed by an impulse in nerve C, regardless of exactly why nerve C fires (see the illustration on the previous page). Thus for the synapse to improve, nerve C need not fire because A fired. Suppose, for example, that a second nerve, B, makes a synapse with C, and the A-to-C synapse is weak and the B-to-C synapse is strong; suppose further that A and B fire at about the same time or that B fires just slightly ahead of A and that C then fires not because of the effects of A but because of the strong effects ofB. In a Hebb synapse, the mere fact that C fires immediately after A makes the A-to-C synapse stronger. We also suppose that if impulses coming in via path A are not followed by impulses in C, the A-to-C synapse becomes weaker.

To apply this model to binocular convergence in the normal animal, we let cell C be binocular, nerve A be from the nondominant eye, and nerve B be from the dominant eye. The nondominant eye is less likely than the dominant eye to fire the cell. The Hebb hypothesis says that the synapse between nerves A and C will be maintained or strengthened as long as an impulse in A is followed by an impulse in C, an event that is more likely to occur if help consistently comes from the other eye, nerve B, at the right time. And that, in turn, will happen if the eyes are aligned. If activity in A is not followed by activity in C, in the long run the synapse between A and C will be weakened. It may not be easy to get direct proof that the Hebb synapse model applies to strabismus, at least not in the near future, but the idea seems attractive.

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THE ANATOMICAL CONSEQUENCES OF DEPRIVATION

Our failure to find any marked physiological defects in geniculate cells, where little or no opportunity exists for eye competition, seemed to uphold the idea that the effects of monocular eye closure reflected competition rather than disuse. To be sure, the geniculate cells were histologically atrophic, but—so we rationalized—one could not expect everything to fit. If competition was indeed the important thing, it seemed that cortical layer 4C might provide a good place to test the idea, for here, too, the cells were monocular and competition was therefore unlikely, so that the alternating left-eye, right-eye stripes should be undisturbed. Thus by recording in long microelectrode tracks through layer 4C, we set out to learn whether the patches still existed after monocular closure and were of normal size. It soon became obvious that 4C was still subdivided into left-eye and right-eye regions, as it is in normal animals, and that the cells in the stripes connected to the eye that had been closed were roughly normal. But the sequences of cells dominated by the closed eye were very brief, as if the stripes were abnormally narrow, around 0.2 millimeter instead of 0.4 or 0.5 millimeter. The stripes belonging to

theopen eye seemed correspondingly wider.
As soon as it became available, we used the anatomical technique of eye injection and transneuronal transport to obtain direct and vivid confirmation of this result. Following a few months' deprivation in a cat or monkey, we injected the good eye or the bad eye with radioactive amino acid. The autoradiographs showed a marked shrinkage of deprived-eye stripes and a corresponding expansion of the stripes belonging to the good eye. The lefthand photograph on this page shows the result of injecting the good eye with radioactive amino acid. The picture, taken, as usual, with dark-field illumination, shows a section cut parallel to the surface and passing through layer 4C. The narrow, pinched-off black stripes correspond to the eye that was closed: the wider light (labeled) stripes, to the open (injected) eye. The converse picture, in which the eye that had been closed was injected, is shown in the photograph on the next page. This section happens to be cut transverse to layer 4C, so we see the patches end-on. These results in layer 4C tended to reinforce our doubts about the competition model, doubts that lingered on because of the geniculate-cell shrinkage: either the competition hypothesis was wrong or something was faulty somewhere in our reasoning. It turned out that the reasoning was at fault for both the geniculate and the cortex. In the cortex, our mistake was in assuming that when we closed the eyes in newborn animals, the ocular-dominance columns were already well developed.

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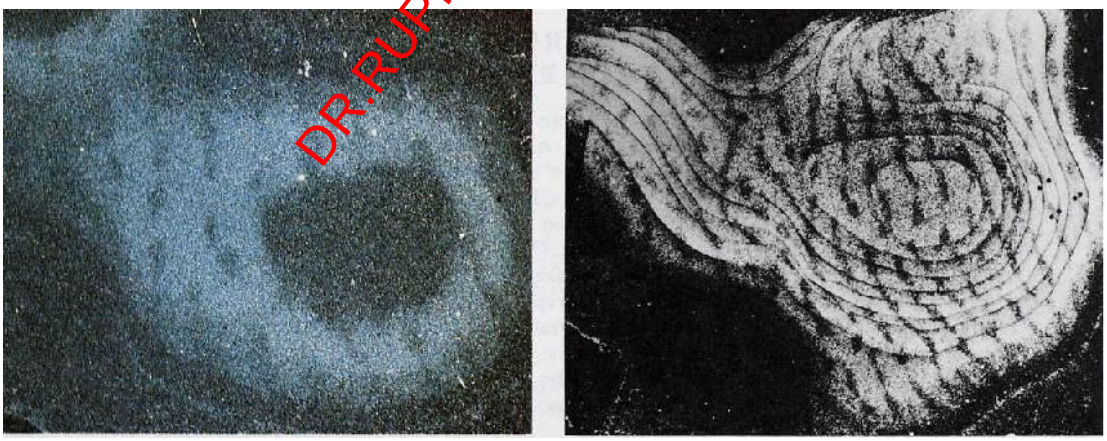
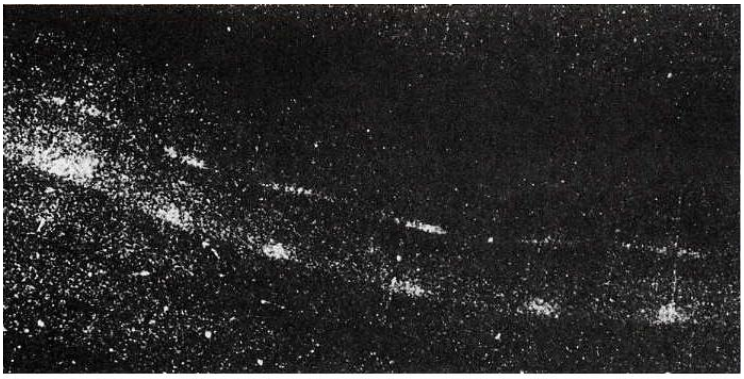
Below: We obtained these sections from a macaque monkey that had an eye sutured closed from birth for eighteen months. The left (open) eye was then injected with radioactive amino acid, and after a week the brain was sectioned parallel to the surface of the visual cortex. (The cortex is dome shaped, so that cuts parallel to the surface are initially tangential, but then produce rings like onion rings, of progressively larger diameter. In the picture on the right, these have been cut from photographs and pasted together. We have since learned to flatten the cortex before freezing it, avoiding the cutting and pasting of serial sections.) In an ordinary photograph of a microscopic section the silver grains are black on a white background. Here we used dark-field microscopy, in which the silver grains scatter light and show as bright regions. The bright stripes, representing label in layer 4C from the open, injected eye, are widened, the dark ones (closed eye), are greatly narrowed.



their final distributions. The faint ripples in the newborn make it clear that the retraction has already begun before birth; in fact, by injecting the eyes of fetal monkeys (a difficult feat) Pasko Rakic has shown that it begins a few weeks before birth. By injecting one eye of monkeys at various ages after birth we could easily show that in the first two or three weeks a steady retraction of fiber terminals



Here, in a different monkey, the closed eye was injected. The section is transverse rather than tangential. The stripes in layer 4C, seen end on and appearing bright in this dark-field picture, are much shrunken.

NORMAL DEVELOPMENT OF EYE-DOMINANCE COLUMNS

The obvious way to learn about ocular-dominance columns in the newborn was to check the distribution of fibers entering layer 4C by injecting an eye on the first or second day of life. The result was surprising. Instead of clear, crisp stripes, layer 4C showed a continuous smear of label. The lefthand autoradiograph on the next page shows 4C cut transversely, and we see no trace of columns. Only when we sliced the cortex parallel to its surface was it possible to see a faint ripple at half-millimeter intervals, as shown in the right-hand autoradiograph. Evidently, fibers from the geniculate that grow into the cortex do not immediately go to and branch in separate left-eye and right-eye regions. They first send branches everywhere over a radius of a few millimeters, and only later, around the time of birth, do they retract and adopt their final distributions. The faint ripples in the newborn make it clear that the retraction has already begun before birth; in fact, by injecting the eyes of fetal monkeys (a difficult feat) Pasko Rakic has shown that it begins a few weeks before birth. By injecting one eye of monkeys at various ages after birth we could easily show that in the first two or three weeks a steady retraction of fiber terminals takes place in layer 4, so that by the fourth week the formation of the stripes is complete. We easily confirmed the idea of postnatal retraction of terminals by making records from layer 4C in monkeys soon after birth. As the electrode traveled along the layer parallel to the surface, we could evoke activity from the two eyes at all points along the electrode track, instead of the crisp eye-alternation seen in adults. Caria Shatz has shown that an analogous process of development occurs in the cat geniculate: in fetal cats, many geniculate cells temporarily receive input from both eyes, but they lose one of the inputs as the layering becomes established. The final pattern of left-eye, right-eye alternation in cortical layer 4C develops normally even if both eyes are sewn shut, indicating that the appropriate wiring can come about in the absence of experience. We suppose that during development, the incoming fibers from the two eyes compete in layer 4C in such a way that if one eye has the upper hand at any one place, the eye's advantage, in terms of numbers of nerve terminals, tends to increase, and the losing eye's terminals correspondingly recede.

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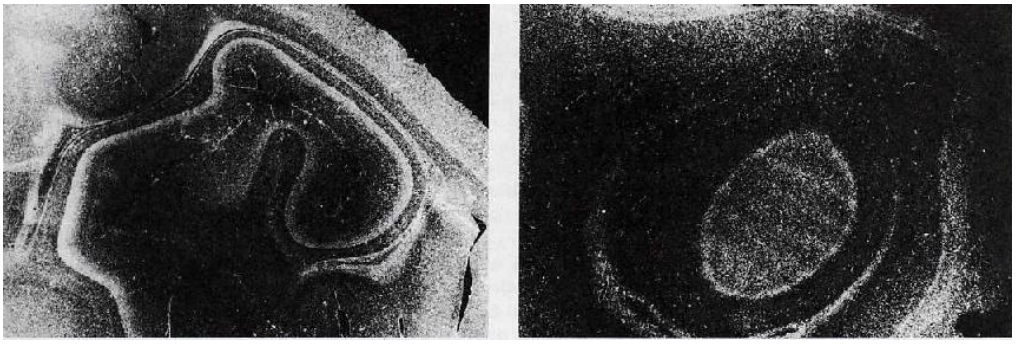

Left: This section shows layer 4C cut transversely, from a newborn macaque monkey with an eye injected. The picture is dark field, so the radioactive label is bright. Its continuity shows that the terminals from each eye are not aggregated into stripes but are intermingled throughout the layer. (The white stripe between the exposed and buried 4C layers is white matter, full of fibers loaded with label on their way up from the lateral geniculates.) *Right*: Here the other hemisphere is cut so that the knife grazes the buried part of the striate cortex. We tan now see hints of stripes in the upper part of 4C. (These stripes are in a subdivision related to the magnocellular geniculate layers. The deeper part, {3, forms a continuous ring around a and so presumably is later in segregating.)

Any slight initial imbalance thus tends to increase progressively until, at age one month, the final punched-out stripes result, with complete domination everywhere in layer 4. In the case of eye closure, the balance is changed, and at the borders of the stripes, where normally the outcome would be a close battle, the open eye is favored and wins out, as shown in the diagram on the next page. We don't know what causes the initial imbalance during normal development, but in this unstable equilibrium presumably even the slightest difference would set things off. Why the pattern that develops should be one of parallel stripes, each a half-millimeter wide, is a matter of speculation. An idea several people espouse is that axons from the same eye attract each other over a short range but that left-eye and right-eye axons repel each other with a force that at short distances is weaker than the attracting forces, so that attraction wins. With increasing distance, the attracting force falls off more rapidly than the repelling force, so that farther away repulsion wins. The ranges of these competing tendencies determine the size of the columns. It seems from the mathematics that to get parallel stripes as opposed to a checkerboard or to islands of left-eye axons in a right-eye matrix, we need only specify that the boundaries between columns should be as short as possible. One thus has a way of explaining the shrinkage and expansion of columns, by showing that at the time the eye was closed, early in life, competition was, after all, possible.

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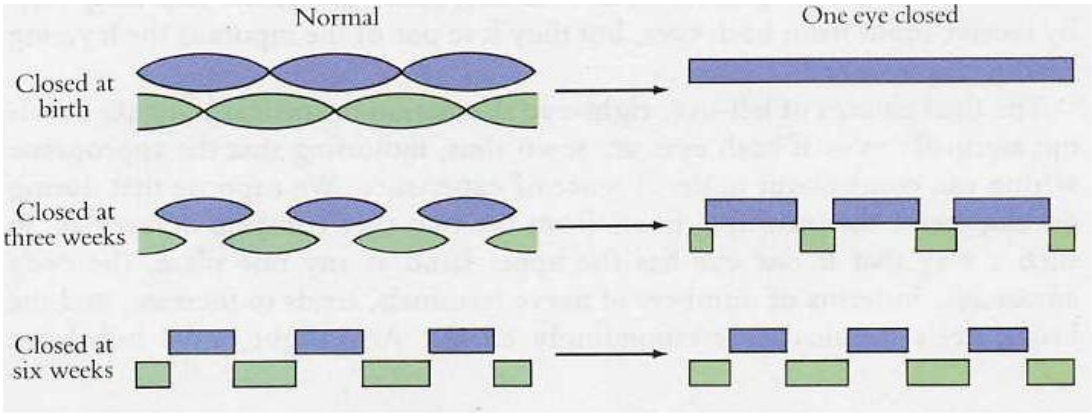

This competition model explains the segre- gation of fourth-layer fibers into eye- dominance columns. At birth the columns have already begun to form. Normally at any given point if one eye dominates even slightly, it ends up with a complete monopoly. If an eye is closed at birth, the fibers from the open eye still surviving at any given point in layer 4 take over completely. The only regions with persisting fibers from the closed eye are those where that eye had no competition when it was closed.

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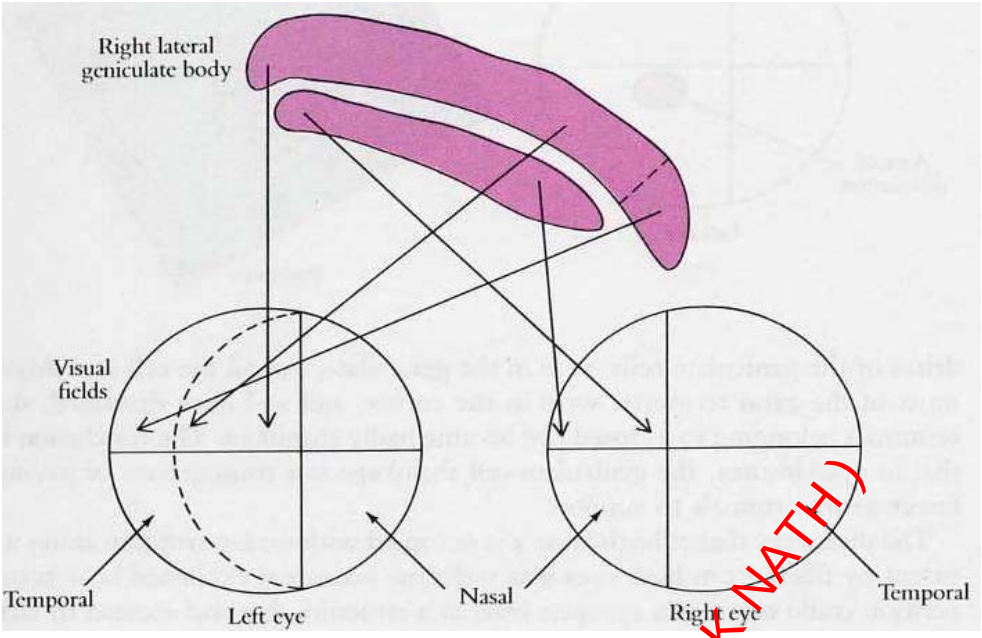
Ray Guillery, then at the University of Wisconsin, had meanwhile produced a plausible explanation for the atrophy of the geniculate cells. On examining our figures showing cell shrinkage in monocularly deprived cats, he noticed that in the part of the geniculate farthest out from the midline the shrinkage was much less; indeed, the cells there, in the temporal-crescent region, appeared to be normal. This region represents part of the visual field so far out to the side that only the eye on that side can see it, as shown in the diagram on this page. We were distressed, to say the least; we had been so busy legitimizing our findings by measuring cell diameters that we had simply forgotten to look at our own pictures. This failure to atrophy of the cells in the geniculate receiving temporal-crescent projections suggested that the atrophy elsewhere in the geniculate might indeed be the result of competition and that out in the temporal crescent, where competition was absent, the deprived cells did not shrink.

By a most ingenious experiment, illustrated in the diagram on the next page, Murray Sherman and his colleagues went on to establish beyond any doubt the importance of competition in geniculate shrinkage. They first destroyed a tiny part of a kitten's retina in a region corresponding to an area of visual field that receives input from both eyes. Then they sutured closed the other eye. In the geniculate, severe cell atrophy was seen in a small area of the layer to which the eye with the local lesion projected. Many others had observed this result. The layer receiving input from the other eye, the one that had been closed, was also, as expected, generally shrunken, except in the area opposite the region of atrophy. There the cells were normal, despite the absence of visual input. By removing the competition, the atrophy from eye closure had been prevented. Clearly the competition could not be in the geniculate itself, but one has to remember that although the cell bodies and den drites of the geniculate cells were in the geniculate, not all the cell was there: most of the axon terminals were in the cortex, and as I have described, the terminals belonging to a closed eye became badly shrunken. The conclusion is that in eye closures, the geniculate-cell shrinkage is a consequence of having fewer axon terminals to support.



The various parts of the two retinas project onto their own areas of the right lateral geniculate body of the cat (seen in cross section). The upper geniculate layer, which receives input from the opposite (left) eye, overhangs the next layer. The overhanging part receives its input from the temporal crescent, the part of the contralateral nasal retina subserving the outer (temporal) part of the visual field, which has no counterpart in the other eye. (The temporal part of the visual field extends out farther because the nasal retina extends in farther). In monocular closure (here, for example, a closure of the left eye), the overhanging part doesn't atrophy, presumably because it has no competition from the right eye.

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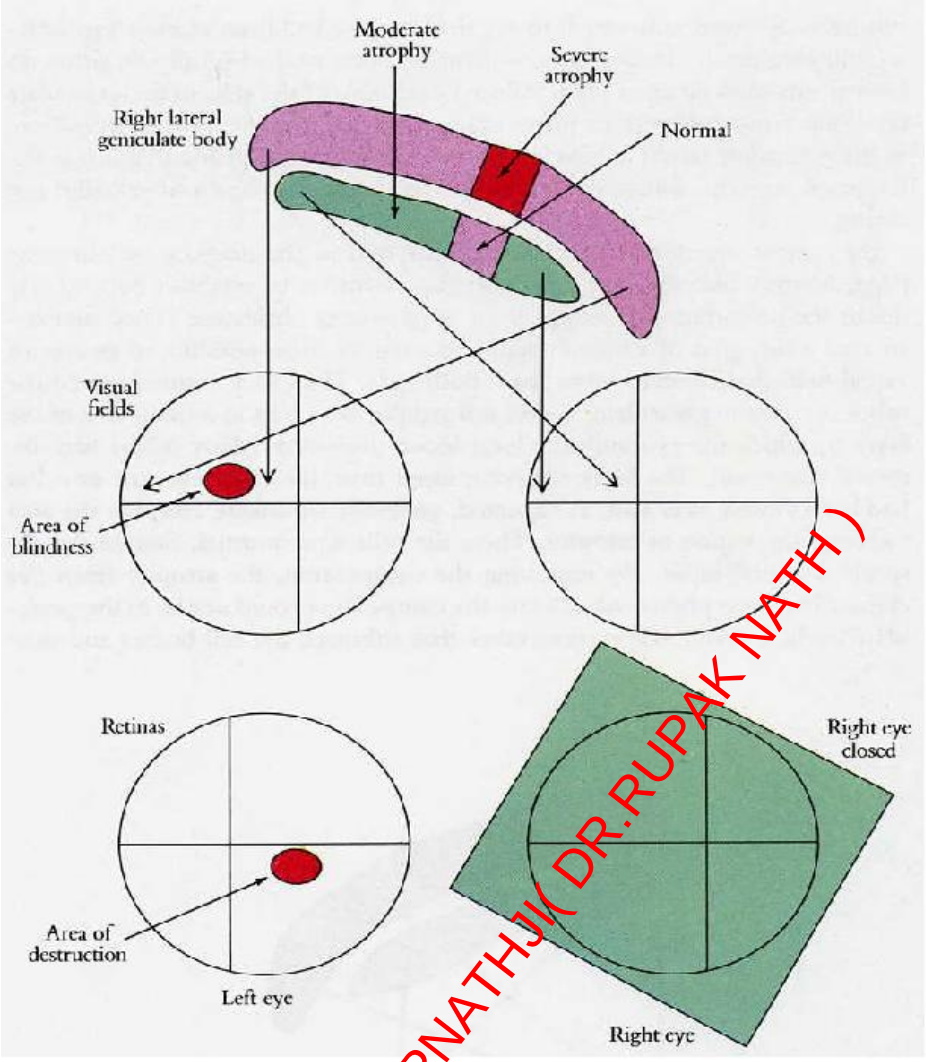
The discovery that at birth layer 4 is occupied without interruption along its extent by fibers from both eyes was welcome because it explained how competition could occur at a synaptic level in a structure that had seemed to lack any opportunity for eye interaction. Yet the matter may not be quite as simple as this. If the reason for the changes in layer 4 was simply the opportunity for competition in the weeks after birth afforded by the mixture of eye inputs in that layer, then closing an eye at an age when the system is still plastic but the columns have separated should fail to produce the changes. We closed an eye at five-and-a-half weeks and injected the other eye after over a year of closure. The result was unequivocal shrinkage-expansion. This would seem to indicate that in addition to differential retraction of terminals, the result can be produced by sprouting of axon terminals into new territory.

FURTHER STUDIES IN NEURAL PLASTICITY

The original experiments were followed by a host of others, carried out in many laboratories, investigating almost every imaginable kind of visual deprivation. One of the first and most interesting asked whether bringing up an animal so that it only saw stripes of one orientation would result in a loss of cells sensitive to all other orientations.



In 1974 an experiment by Sherman, Guillery, Kaas and Sanderson demonstrated the importance of competition in geniculate-cell shrinkage. If a small region of the l left retina of a kitten is destroyed, there results an island of severe atrophy in the corresponding part of the upper layer of the right lateral geniculate body. If the right eye is then closed, the layer below the dorsal layer, as expected, becomes atrophic—except for the region immediately opposite the upper-layer atrophy, strongly suggesting a competitive origin for the atrophy resulting from eye closure.

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In 1970 Colin Blakemore and G. F. Cooper, in Cambridge University, exposed kittens from an early age fora few hours each day to vertical black-and-white stripes but otherwise kept them in darkness. Cortical cells that preferred vertical orientation were preserved, but cells favoring other orientations declined dramatically in number. It is not clear whether cells originally having non-vertical orientations became unresponsive or whether they changed their preferences to vertical. Helmut Hirsch and Nico Spinelli, in a paper published the same year, employed goggles that let the cat see only vertical contours through one eye and only horizontal contours through the other. The result was a cortex containing cells that preferred verticals and cells that preferred horizontals, but few that preferred obliques. Moreover, cells activated by horizontal lines were influenced

only by the eye exposed to the horizontal lines, and cells driven by vertical lines, only by the eye exposed to the vertical lines. Other scientists have reared animals in a room that was dark except for a bright strobe light that flashed once or a few times every second; it showed the animal where it was but presumably minimized any perception of movement. The results of such experiments, done in 1975 by Max Cynader, Nancy Berman, and Alan Hein, at MIT, and by Max Cyander and G. Chernenko, at Dalhousie in Halifax, were all similar in producing a reduction of movement-selective cells. In another series of experiments by F. Tretter, Max Cynader, and Wolf Singer in Munich, animals were exposed to stripes moving from left to right; this led to the expected asymmetrical distribution of cortical direction-selective cells.

It seems natural to ask whether the physiological or anatomical changes produced by any of these deprivation experiments serve a useful purpose. If one eye is sewn closed at birth, does the expansion of the open eye's terrain in layer 4C confer any advantage on that eye? This question is still unanswered. It is hard to imagine that the acuity of the eye becomes better than normal, since ordinary acuity, the kind that the ophthalmologist measures with the test chart, ultimately depends on receptor spacing (Chapter 3), which is already at the limits imposed by the wavelength of light. In any case it seems most unlikely that such plasticity would have evolved just in case a baby lost an eye or developed strabismus. A more plausible idea is that the changes make use of a plasticity that evolved for some other function—perhaps for allowing the postnatal adjustments of connections necessary for form analysis, movement perception and stereopsis, where vision itself can act as a guide. Although the deprivation experiments described in this chapter exposed animals to severely distorted environments, they have not involved direct assaults on the nervous system: no nerves were severed and no nervous tissue was destroyed. A number of recent studies have indicated that with more radical tampering even primary sensory areas can be rewired so as to produce gross rearrangements in topography. Moreover, the changes are not confined to a critical period in the early life of the animal, but can occur in the adult. Michael Merzenich at the University of California at San Francisco has shown that in the somatosensory system, after the nerves to a limb are severed or the limb amputated, the region of cortex previously supplied by these nerves ends up receiving input from neighboring areas of the body, for example from regions of skin bordering on the numb areas. A similar reorganization has been shown to occur in the visual system by Charles Gilbert and his colleagues at the Rockefeller University. They made small lesions in corresponding locations in the two retinas of a cat; when they later recorded from the area of striate cortex to which the damaged retinal areas had projected, they found that, far from being unresponsive, the cells responded actively to regions of retina adjacent to the damaged regions. In both these sets of experiments the cortical cells deprived of their normal sensory supply do not end up high and dry, but acquire new inputs. Their new receptive fields are much larger than normal, and thus by this measure the readjustments are crude. The changes seem to result in part from a heightening of the sensitivity of connections that had been present all along but had presumably been too weak to be easily detected, and in part from a subsequent, much slower development of new connections by a process known as nerve sprouting. Again it is not clear what such readjustments do for the animal; one would hardly expect to obtain a heightening of perception in the areas adjacent to numb or blind areas— indeed, given the large receptive fields, one would rather predict an' impairment.

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THE ROLE OF PATTERNED ACTIVITY IN NEURAL DEVELOPMENT

Over the past few years a set of most impressive advances have forced an entire rethinking of the mechanisms responsible for the laying down of neural connections, both before and after birth. The discovery of orientation selectivity and orientation columns in newborn monkeys had seemed to indicate a strongly genetic basis for the detailed cortical wiring. Yet it seemed unlikely that the genome could contain enough information to account for all that specificity. After birth, to be sure, the visual cortex could fine-tune its
neural connections in response to the exigencies of the environment, but it was hard to imagine how any such environmental molding could account for preatal wiring.

Our outlook has been radically changed by a heightened appreciation of the part played in development by neural activity. The strabismus experiments had pointed to the importance of the relative timing of impulses arriving at the cortex, but the first direct evidence that firing was essential to the formation of neural connections came from experiments by Michael Stryker and William Harris at Harvard Medical School in 1986. They managed to eliminate impulse activity in the optic nerves by repeatedly injecting tetrodotoxin (a neurotoxin obtained from the putter fish) into the eyes of kittens, over a period beginning at age 2 weeks and extending to an age of 6 to 8 weeks. Then the injections were discontinued and activity was allowed to resume. By the eighth week after birth the ocular dominance columns in cats normally show clear signs of segregation, but microelectrode recordings indicated that the temporary impulse blockade had prevented the segregation completely. Clearly, then, the segregation must depend on impulses coming into the cortex. In another set of experiments Stryker and S. L. Strickland asked if it was important for the activity of impulses in optic-nerve fibers to be synchronized, within each eye and between the two eyes. They again blocked optic-nerve impulses in the eyes with tetrodotoxin, but this time they electrically stimulated the optic nerves during the entire period of blockage. In one set of kittens they stimulated both optic nerves together and in this way artificially synchronized inputs both within each eye and between the eyes. In these animals the recordings again indicated that the formation of ocular dominance columns had been completely blocked. In a second set of kittens they stimulated the two nerves alternately, shocking one nerve for 8 seconds, then the other. In this case the columns showed an exaggerated segregation similar to that obtained with artificial strabismus. The normal partial segregation of ocular dominance columns may thus be regarded as the result of two competing processes: in the first, segregation is promoted when neural activity is syn- chronized in each eye but not correlated between the eyes; and in the second, binocular innervation of neurons and merging of the two sets of columns is promoted by the synchrony between corresponding retinal areas of the two eyes that results from normal binocular vision.

Caria Shatz and her colleagues have discovered that a similar process occurs prior to birth in the lateral geniculate body. In the embryo the two optic nerves grow into the geniculate and initially spread out to occupy all the layers. At this stage many cells receive inputs from both eyes. Subsequently segregation begins, and by a few weeks before birth the two sets of nerve terminals have become confined to their proper layers. The segregation seems to depend on spontaneous activity, which has been

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shown by Lamberto Maffei and L. Galli-Resta to be present in fetal optic nerves, even before the rods and cones have developed. Shatz and her colleagues showed that if this normal spontaneous firing is suppressed by injecting tetrodotoxin into the eyes of the embryo, the segregation into layers is prevented.

Further evidence for the potential importance of synchrony in development of neuronal connections comes from work at Stanford by Dennis Baylor, Rachel Wong, Marcus Meister, and Caria Shatz. They used a new technique for recording simultaneously from up to one hundred retinal ganglion cells. They found that the spontaneous firing of ganglion cells in fetal retinas tends to begin at some focus in the retina and to spread across in a wave. Each wave lasts several seconds and successive waves occur at intervals of up to a minute or so, starting at random from different locations and proceeding in random directions. The result is a strong tendency for neighboring cells to fire in synchrony, but almost certainly no tendency for cells in corresponding local areas of the two retinas to fire in synchrony. They suggest that this local retinal synchrony, plus the lack of synchrony between the two eyes, may form the basis for the layering in the lateral geniculate, the ocular dominance columns in the cortex, and the detailed topographic maps in both structures. Shatz has summed up the idea by the slogan "Cells that fire together wire together".

This concept could explain why, as discussed in Chapter 5, nerve cells with like response properties tend to be grouped together. There the topic was the aggregation of cells with like orientation selectivities into orientation columns, and I stressed the advantages of such aggregation for economy in lengths of connections. Now we see that it may be the synchronous firing of the cells that promotes the grouping. How, then, do we account for the fact that connections responsible for orientation selectivity are already present at birth, without benefit of prior retinal stimulation by contours? Can we avoid the conclusion that these connections, at least, must be genetically determined? It seems to me that one highly speculative possibility is offered by the waves of activity that criss-cross the fetal retina: if each wave spreads out from a focus, a different focus each time, perhaps the advancing fronts of the waves supply just the oriented stimuli that are required to achieve the appropriate synchrony—an oriented moving line. One could even imagine testing such an idea by stimulating the fetal retina to produce waves that always spread out from the same focus, to see if that would lead to all cortical cells having the same orientation selectivity.

All of this reinforces the idea that activity is important if competition is to take place. This is true for the competition between the two eyes that occurs in normal development, and the abnormal competition that occurs in deprivation and strabismus. Beyond that, it is not just the presence or absence of activity that counts, but rather the patterns of synchronization of the activity.

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THE BROADER IMPLICATIONS OF DEPRIVATION RESULTS

The deprivation experiments described in this chapter have shown that it is possible to produce tangible physiological and structural changes in the nervous system

by distorting an animal's experience. As already emphasized, none of the procedures did direct damage to the nervous system; instead the trauma was environmental, and in each case, the punishment has more or less fit the crime. Exclude form, and cells whose normal responses are to forms become unresponsive to them. Unbalance the eyes by cutting a muscle, and the connections that normally subserve binocular interactions become disrupted. Exclude movement, or movement in some particular direction, and the cells that would have responded to these movements no longer do so. It hardly requires a leap of the imagination to ask whether a child deprived of social contacts—left in bed all day to gaze at an orphanage ceiling—or an animal raised in isolation, as in some of Harry Harlow's experiments, may not suffer analogous, equally palpable changes in some brain region concerned with relating to other animals of the same species. To be sure, no pathologist has yet seen such changes, but even in the visually deprived cortex, without very special methods such as axon-transport labels or deoxyglucose, no changes can be seen either. When some axons retract, others advance, and the structure viewed even with an electron microscope continues to look perfectly normal. Conceivably, then, many conditions previously categorized by psychiatrists as "functional" may turn out to involve organic defects. And perhaps treatments such as psychotherapy may be a means of gaining access to these higher brain regions, just as one tries in cases ofstrabismic amblyopia to gain access to the striate cortex by specific forms of binocular eye stimulation. Our notions of the possible implications of this type of work thus go far beyond the visual system—into neurology and much of psychiatry. Freud could have been right in attributing psychoneuroses to abnormal experiences in childhood, and considering that his training was in neurology, my guess is that he would have been delighted at the idea that such childhood experiences might produce tangible histological or histochemical changes in the real, physical brain.

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