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23. We thank participants in the Precambrian Paleobiology Research Group (PPRG) fieldwork of June 1982: K. J. Armstrong, D. Blight, D. J. Chapman, J. M. Hayes, A. H. Hickman, C. Klein, D. D. Radke, J. C. G. Walker, and M. R. Walter. For review of this manuscript, we thank S. M. Awramik, J. Lake, T. Moore, J. Shen-Miller, G. Vidal, and M. R. Walter. The 1982 fieldwork was supported by NASA grant NGW-825 to the PPRG. The 1986 fieldwork was supported by NASA grant NGR-05-007-407 to J.W.S. and by both the Western Australia Geological Survey, Perth, and the Bureau of Mineral Resources, Canberra, to which organizations we are grateful. Laboratory studies supported by NSF grant BMR 79-21777 to J.W.S.

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# Local Retinal Regions Control Local Eye Growth and Myopia

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**In chicks, visual deprivation leads to myopia and enlargement of the vitreous chamber of the eye. When chicks were raised with white translucent occluders over their eyes so that either the nasal half, the temporal half, or all of the retina was visually deprived, the resulting myopia (median = −15 diopters) was limited to the deprived part of the retina, regardless of which half of the retina was visually deprived; the nondeprived part remained nearly emmetropic. Correspondingly, the vitreous chamber was elongated only in the region of the visual deprivation, resulting in eyes with different asymmetric shapes depending on which retinal region was deprived. These results argue for a local regulation of ocular growth that is dependent on vision and suggest a hypothesis to explain the epidemiological association of myopia in humans with large amounts of reading. Because most nonfoveal retinal neurons have large receptive fields, they cannot resolve the individual letters on the printed page; this may lead to their activity being less during reading than during most other forms of visual stimulation. Thus, the impoverished stimulus situation of reading may lead to myopia, as do other types of visual form deprivation.**

IN MOST ANIMALS THE OPTICAL POWER of the eyes is well matched to their length so that images of distant objects are in focus on the retina (emmetropia). In humans, however, this matching of optical power and eye size is frequently lacking. This results in significant degrees of myopia (nearsightedness) if the eye is too long compared with its optical power, or hyperopia (farsightedness) if the eye is too short. At birth, eyes of several species are hyperopic and very variable in refractive status but quickly grow toward emmetropia (*1*). This raises the possibility that myopia and hyperopia may reflect disorders of the emmetropization process. Various hypotheses, some rather curious, involving dietary, hormonal, occupational, and psychological causes of myopia have enjoyed periods of popularity, as have a variety of mechanisms of myopia involving, for example, eyestrain, accommodation, convergence, inflammation, traction on the optic nerve, and pressure on the veins leaving the eye (*2*).

Within the past decade, it has become clear that alterations in visual experience can provoke myopia: monkeys, tree shrews, and probably cats become myopic when deprived of form vision early in life (*3–6*). In these cases, as in typical human myopia (*7, 8*), the myopia involves an increase in the length of the eye. Children also have been found to become myopic when deprived of form vision because of a variety of disorders that have in common an obstruction of vision, such as ptosis, hemangiomas, or congenital cataracts (*9, 10*).

These demonstrations that an aspect of vision could influence myopia have been seen as consistent with the view that typical human myopia is due to an excess of ocular accommodation (the focusing of the eye for near distances) caused by long periods of near viewing, as in reading. The principal support for this hypothesis has come historically from observations that professions requiring much reading or other close work tend to be occupied by myopes, and that there is a consistent correlation between educational level and degree of myopia (*11*). In addition, one study in an Inuit community suggested that the advent of compulsory schooling, along with other accoutrements of Western civilization, was associated with an increased incidence of myopia (*12*). A long history of observations such as these has entrenched the idea that near work is a primary factor in the etiology of myopia.

Some animal research also supports an association of increased accommodation and myopia. Young reported that a small amount of myopia was produced by restricting the vision of monkeys to white drapes 18 inches away (*13*). Evidence of an effect of near vision was also suggested, but not proven, by studies showing that cage-reared cats and monkeys (*14*) are myopic compared with wild conspecifics. Of course, many differences other than the amount of near vision distinguish wild from captive animals. Chimpanzees raised in cages show a progression toward greater myopia as they get older, presumably as a result of captivity (*15*).

The results of experimental tests of the accommodation hypothesis are equivocal. There are some positive results showing reduced progression of myopia when children or animals are given daily doses of atropine, a drug that paralyzes the muscles of accommodation (*16, 17*). On the other hand, an equally careful study, in which the need for accommodation was reduced by having children wear bifocals, produced no change in myopic progression (*18*). Denervation of the ciliary muscles in chicks reduced, but did not eliminate, myopia caused by visual deprivation (*19*). Recently, Raviola and Wiesel have mentioned in a review

**Table 1.** Median refractive error of three locations of visually deprived eyes.

| Deprived area | *n* | Median refractive error (diopters) | | |
|---|---|---|---|---|
| | | Nasal retina | Optic axis | Temporal retina |
| Nasal retina | | | | |
| 2 weeks | 30 | −13.6 | −7.7 | +0.8 |
| 6 weeks | 21 | −9.1 | −5.5 | +0.8 |
| Temporal retina | | | | |
| 2 weeks | 26 | −2.6 | −15.0 | −17.7 |
| 6 weeks | 20 | +1.7 | −1.7 | −10.2 |
| Total retina | | | | |
| 2 weeks | 19 | −20.2 | −28.4 | −28.1 |
| 6 weeks | 18 | −18.6 | −22.7 | −17.6 |

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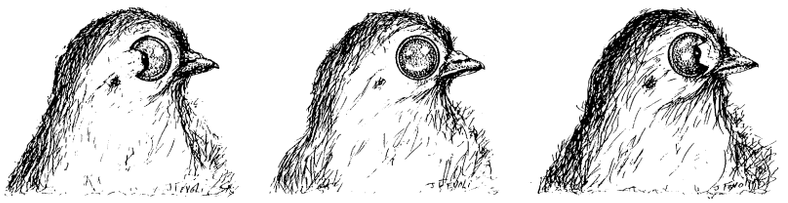

**Fig. 1.** Treatments used to restrict visual experience to part of the retina. Temporal retina is visually deprived in animal on left, nasal retina in animal on right, and all of retina in center animal.

that neither atropine nor optic nerve section prevent visual deprivation from producing myopia in rhesus monkeys, although either procedure is effective in the stumptail macaque (*17*).

The various hypotheses of the etiology of myopia that have attracted serious attention all have one attribute in common: They appear to act on the eye as a whole to produce a "global myopia." We present evidence here that form deprivation of one region of the retina produces myopia only in that region and produces a corresponding local change in the shape of the globe. We also propose a hypothesis for how local visual deprivation might account for "near-work myopia" in humans.

Our experiment was based on three previous studies that showed that (i) chicks raised with vision restricted to the frontal visual field become severely myopic (*4*); (ii) the myopia does not extend to the frontal visual field (*20*); and (iii) this "local myopia" involves corresponding local changes in the shape of the posterior wall of the eye (*21*). Our experiment tests the suggestion of Hodos and Kuenzel (*22*) that different regions of the eye could become myopic independently.

Chicks were raised from hatching with one of three visual restrictions of one eye. Either they were totally deprived of form vision by means of white translucent plastic occluders placed over their eyes, or only the nasal or temporal retina was deprived of vision by means of the same occluders with a trapezoidal window (Fig. 1). In all groups, the deprivation included the retinal region near the optic axis (*23*).

At 2 and 6 weeks of age, the occluders were removed and the refractive status of the eyes determined with a Hartinger Refractometer. All refractions were done under cycloplegia and were masked so that the refractionist did not know which birds had which visual restriction. To evaluate local differences in refractive status, measurements were made along three different lines of sight: along the optic axis, 30° nasal to and 30° temporal to the optic axis (*24*).

In eyes in which only the nasal retina was visually deprived, only the nasal retina became very myopic; in eyes in which only the temporal retina was deprived, only the temporal retina became very myopic (Fig. 2 and Table 1). In both cases, the part of the retina near the optic axis, which had visual experience whenever the bird moved its eye by more than about 11°, was less myopic, and the visually unrestricted region was hardly myopic at all. Eyes with total form deprivation were myopic in all three retinal regions. For both partial visual deprivations and at both ages, the difference in refractive status between the nasal and temporal regions was significant (Wilcoxon test, $P < 0.01$, $n > 20$ for all comparisons). Because the deprived retinal regions became severely myopic regardless of which retinal region was deprived, these results are not attributable to differences in susceptibility to myopia of different regions nor to a greater efficacy of one or the other type of restriction.

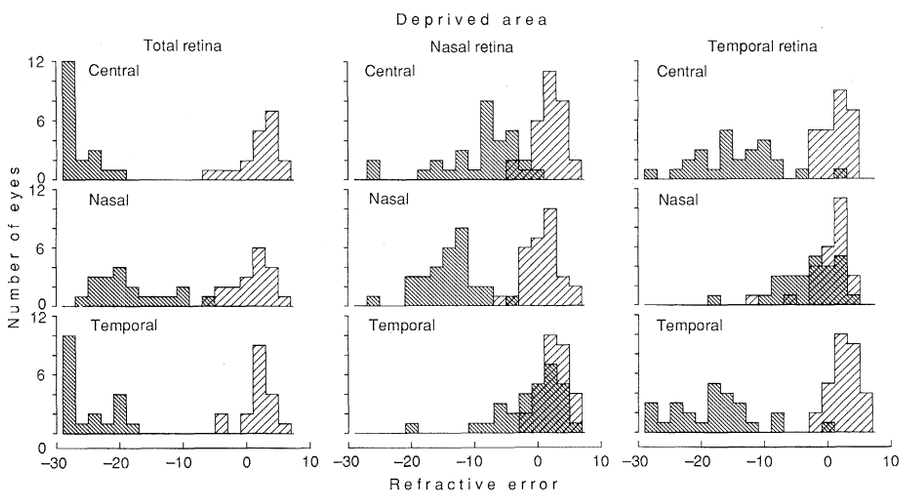


**Fig. 2.** Ocular refractions along three axes of measurement of 2-week-old visually deprived animals. Negative values denote myopia; dense shading denotes the experimental eye and light shading the control eye. Note that only the deprived retinal regions become myopic.

In chicks, as in other species studied, the myopia resulting from visual deprivation is associated with an increase in the depth of the vitreous chamber (*4, 5, 22, 25*). To determine whether the refractions we measured corresponded to changes in the shape of the eye, which produced differences in the optical length of the vitreous chamber along different lines of sight, we photographed the eyes of these birds after taking the refractive measurements at 2 and 6 weeks of age (*26*). To characterize the shape of these eyes, their outlines were digitized, aligned with each other, and averaged (*27*).

In the eyes with visual deprivation of the nasal retina, the nasal portion of the vitreous chamber was enlarged, but the temporal part was like that of the other (untreated) eye (Fig. 3). Similarly, in the eyes with visual deprivation of the temporal retina, only the temporal region of the eye was enlarged. In the eyes with total visual deprivation, the entire posterior wall of the eye was enlarged. We evaluated these results statistically in two ways. To show the individual variation in ocular asymmetry, we divided each of 26 radii in the nasal half of the posterior sclera (10° to 60° from the optic axis) by the corresponding radius in the temporal half and averaged the resulting quotients (Fig. 4A). There was almost no overlap between the two groups with partial visual deprivation. Even when compared to controls, both groups are significantly different ($P < 0.01$, two-tailed $t$ test). By comparing each experimental eye to the fellow control eye, we showed the degree of elongation at each angle by dividing each radius from the posterior half of each experimental eye by the corresponding radius from the control eye of the same animal and averaging across animals. The resulting contours (Fig. 4B) differ substantially among experimental groups. (At 30° to either side of the optic axis, the two partially restricted groups each differed: $t(18) = 10.16$, and $t(20) = 8.03$, $P < 0.0001$.)

Our results imply that regions of the retina can control the growth of the subjacent sclera. These results indicate that myopia cannot be attributed entirely to global processes such as altered intraocular pressure or accommodation (*28*). Because optic nerve section neither prevents the development of myopia in chicks (*29*), or, as men-

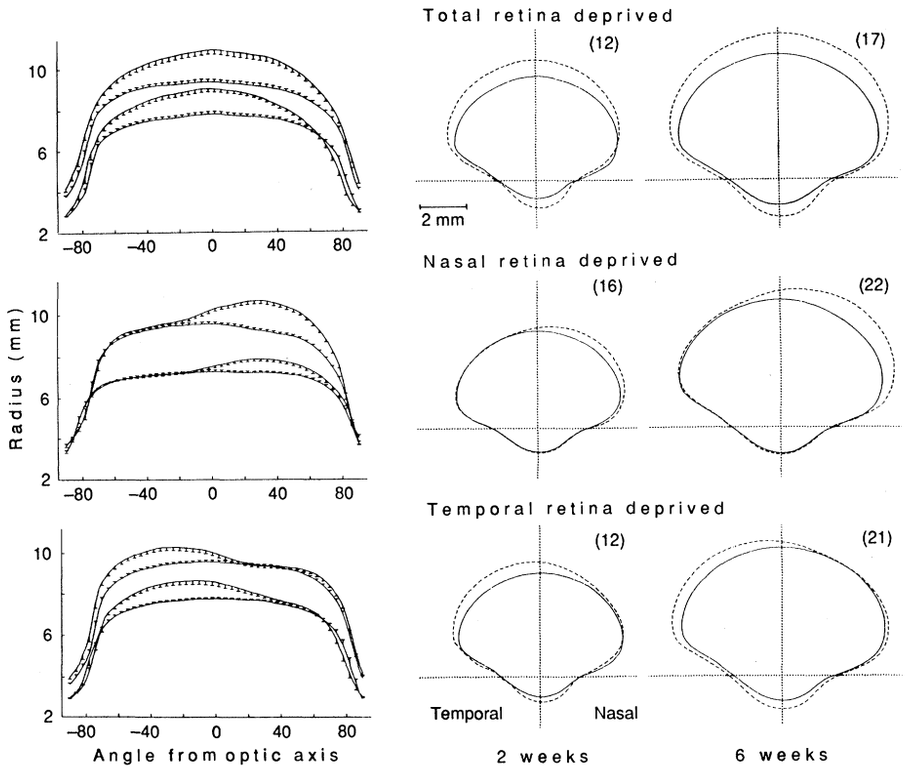


**Fig. 3.** Effects of visual deprivations on shape of eyes. (**Right**) Averages traced from photographs; the interrupted line is the deprived eye; the solid line is the control eye from the same animals. All eyes are presented as right eyes, viewed from above. The "optic axis" is defined here as the perpendicular bisecting the line joining the corneal margins. (**Left**) Radii measured from the intersection of these lines. Downward error bars (SEM) are deprived eye; upward error bars are control eyes. Nasal angles are positive. Eyes become enlarged only in the regions of retinal visual deprivation. The greater effect of visual deprivation of the nasal retina may be due to their smaller visual fields. Note the deep anterior chambers in eyes with total or temporal deprivation. Alternate data points have been omitted for clarity.

tioned above, in rhesus monkeys (*17*), nor does it prevent the local growth changes reported here (*30*), these changes in eye shape cannot be attributed to differences in eye movements with different occluders. Work in progress indicates that 10-Hz strobe light protects partially deprived eyes from this local myopia, presumably by enhancing local retinal activity.

During normal development, retinal regions may independently adjust the optical path length for different parts of the eye in the direction of emmetropia. This control may be accomplished by secretion of humoral growth modulators, since the retina is known to secrete factors that promote growth of scleral fibroblasts and factors that inhibit such growth (*31*). Because both human infants and newly hatched chicks tend to be hyperopic, developmental control of ocular growth might be mediated either by the secretion of scleral growth promoters when vision is blurred or by the secretion of scleral growth inhibitors when clear vision is attained, leading in either case to the eye stabilizing at emmetropia.

Variation in refractive state across the retina occurs in several species, including humans (*32*). In humans the pattern of variation differs in emmetropes, myopes, and hyperopes (*33*). In pigeons, the lower visual field, which habitually views the ground, is myopic in precise proportion to its customary distance to the ground (*34*). The influence of vision on local retinal control of eye growth during ontogeny might account for all of these variations in refractive error with retinal location.

Our results lead us to suggest the hypothesis that the two experiential conditions strongly linked to myopia in humans and animals—large amounts of reading and deprivation of form vision—both cause myopia by visual deprivation. Although the printed page may provide adequate stimulation for the foveal retina, it could provide an impoverished stimulus environment for other regions of the retina, resulting in myopia.

It can be argued that the activity of nonfoveal retinal neurons is lower during reading. Most retinal neurons have transient responses, but normally the movements of the eyes provide these neurons with continually changing stimuli, which renew their responses. If a neuron received exactly the same stimulus pattern before and after the eye movement, its activity would presumably decay to zero. Thus, the activity of retinal neurons averaged over a period of time would depend on the differences between successive stimuli received as the eye's movements present the neuron with different pieces of the scene being viewed. Three peculiarities of the printed page act to reduce the variation in stimulation that retinal neurons receive as a result of eye movements.

1) Whereas most scenes are made up of features that vary widely in size (that is, containing a broad range of spatial frequencies), printed text contains mainly small features (that is, high spatial frequencies). Nonfoveal neurons, because they have large receptive fields, cannot resolve the features of individual letters; rather, they respond to the local luminance averaged over several letters. Thus, during reading the activity of nonfoveal neurons changes little with

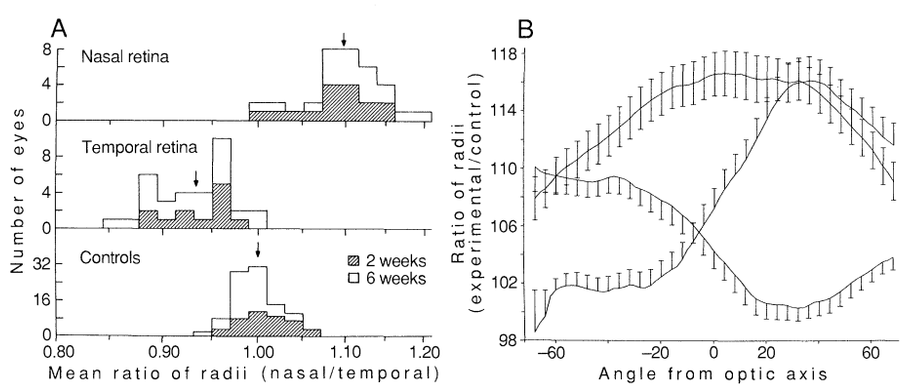


**Fig. 4.** Comparison of shapes of eyes with different deprivations. (**A**) Distribution of degree of asymmetry in individual eyes of each group. Each radius from 10° to 60° on the nasal side of the optic axis was divided by the radius at the same angle on the temporal side. Results are plotted on a logarithmic abscissa. Normal eyes tend to be symmetric; nearly every deprived eye is elongated on the deprived side. (**B**) Ratios of radii of deprived eye divided by those of control eye at each angle. Eyes with nasal retina visually deprived (upward standard error bars) differ in shape from those with temporal retina deprived (downward error bars) and from those with total visual deprivation (complete error bars). As above, nasal angles are positive.

changes in eye position. Only in the fovea, where the neuronal receptive fields are comparable in size to the elements of the letters, will the responses change greatly. In contrast, because the heterogeneous stimuli of most scenes in the natural world include stimuli appropriate in size for neurons at different distances from the fovea, each eye movement would generally present most neurons with a substantially changed level of stimulation (*35*). The cover photograph simulates the output of retinal ganglion cells viewing text (*36*). The center contains "neurons" with smaller receptive fields, which resolve smaller elements than those in the periphery. If one imagines the simulated eye moving slightly, the activity of the "neurons" in the center would change greatly regardless of the material viewed, whereas those in the periphery would hardly change when viewing text.

2) The range of luminances present on the printed page is much smaller than is typical in outdoor scenes. White paper reflects only about ten times the light of black ink, whereas sunny surfaces may be many orders of magnitude brighter than deep shadows. This smaller range of luminance means that the response of neurons changes less from one eye position to the next; this also would lead to lower average neural activity.

3) Text is achromatic, whereas most scenes contain a variety of colors. This may exacerbate the temporal effects, because the most numerous retinal ganglion cells (the inputs to parvocellular lateral geniculate neurons) show transient responses with a rapid time course to noncolored stimuli, in contrast to a much slower decay to chromatic stimuli (*37*). Thus, during reading, the cell's response would fade very rapidly after each eye movement, whereas in viewing typical colored stimuli the response would be more enduring.

Ours is not the first suggestion that visual deprivation of the nonfoveal retina leads to myopia. Low vision patients with disorders affecting the entire retina become myopic, whereas those with conditions principally affecting the foveal region remain hyperopic (*10*). Also, cats and monkeys raised wearing optically strong contact lenses 8 hours daily do not develop myopia (*38*), even though the optical blur is sufficient to produce amblyopia (*39*). We surmise that in these cases reducing the high spatial frequency content, thereby affecting primarily the fovea, did not cause myopia, whereas elimination of all form vision did. Our suggestion could lend credibility to the popular belief that reading in poor light is particularly bad for one's eyes because retinal neurons exhibit lower signal-to-noise ratios in dim light, even well into the photopic range (*40*).

Conceivably, the differences in ocular refraction among people with similar visual habits may be caused by a large variation in the efficacy of the mechanism of visual modulation of eye growth. Those at the low end of the range would tend to remain hyperopic, as they were at birth, and these individuals would also tend to be unaffected by visual environments that lead to myopia; this would account for the fact that hyperopes tend not to become myopic after childhood. In contrast, those with more effective mechanisms of visual modulation of eye growth would become emmetropic at an early age and for the same reason would be particularly susceptible to visual environments that might lead toward myopia.

Although form deprivation explicitly produces local eye growth in chicks and may account for the association of reading and myopia in humans, the retinal cells involved need not be form-sensitive. Any cell with transient responses would be more active in a varied environment because eye movements would continually change the level of stimulation. Thus even non-neuronal cells, such as Mueller cells or pigment epithelium cells, might be less active if the eye wore an occluder or if the scene viewed were uniform. If production of a growth-affecting substance depended on activity, myopia might result.

Finally, although local ocular factors are sufficient to produce local growth and myopia, we suspect that other factors, perhaps including accommodation, may also be important both in emmetropization and in the etiology of myopia.

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24. The eye was aligned by centering in the chick's pupil the image of a circular fluorescent light concentric with the optic axis of the refractometer. To measure the off-axis points, the animal, with its pupil centered on a machinist's turntable, was rotated 30°, measured, and returned to the on-axis position. In all cases at least four pairs of refractions along orthogonal meridians were measured for each eye. The median of the equivalent mean spherical refraction of each pair of measurements is the datum presented here [see (*20*) for details of the methods].
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26. Eyes were enucleated postmortem from Formalin-perfused birds, cleaned, and photographed from above; marks made on the dorsal limbus permitted positioning eyes to within approximately 10° of their normal orientation.
27. Two alignments were performed. First, we aligned four separate tracings of each eye along the equatorial diameter of the eye with an iterative procedure; if the four sets of measurements on each eye were similar enough, the average of each 2° estimate of the radius was used to define the shape. To align different eyes for averaging, we superimposed the midpoints of the line segment joining the two points representing the corneal margins and rotated the eye so that this line was horizontal.
28. In principle, there is no reason why the meridional ciliary muscle fibers could not contract differentially on different sides of the eye and thereby exert differential forces on the nasal and temporal choroid, which could in turn influence scleral growth. Van Alphen (*7*) and McKanna [J. A. McKanna and V. A. Casagrande, *Doc. Ophthalmol. Proc. Ser.* **28**, 187 (1981)] have both discussed the possibility of choroid-mediated mechanisms by which changes in accommodative state could produce refractive error changes.

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35. The relevant factor is the size of saccades relative to the size of the stimuli after filtering by the spatial characteristics of the neuron. Since most saccades during either free-viewing or reading are larger than most retinal receptive fields [A. T. Bahill, D. Adler, L. Stark, *Invest. Ophthalmol. Visual Sci.* **14**, 468 (1975); D. Heller and A. Heinisch, in *Eye Movements and Human Information Processing*, R. Groner, G. W. McConkie, C. Menz, Eds. (Elsevier, New York, 1985)], the distribution of spatial frequencies in the visual scene is the more important variable.
36. Each point on this figure is an estimate of the output of a retinal ganglion cell with the center of its receptive field at that point. Each receptive field is treated as an excitatory central process and an inhibitory surround process, both Gaussian in shape, with the receptive field diameter declining linearly with distance from the fovea. To obtain each point, Dr. C. M. Harris and I multiplied the brightness of the scene at each location in each receptive field by the height at that point of the curve representing the difference between the influence of the excitatory center and the inhibitory surround and summed all of these points. The result of these computations constitutes what might be called the "ganglion cells' view" of the scene. For printed text, the image is distinct only around the fovea and becomes blurred quite quickly with distance from the fovea. For the change in receptive field size with eccentricity, we used the figures of Blakemore and Vital-Durand [C. Blakemore and F. Vital-Durand, *Trans. Ophthalmol. Soc. U.K.* **99**, 363 (1979)] for the lateral geniculate neurons of the rhesus monkey, but multiplied by 1.33 to reflect the larger size of human eyes. For the size of the foveal receptive fields, we used 0.02°. For the shape of the center and surround processes, we considered the surround to have an area ten times that of the center and a total influence half as great as the center (Robert Shapley, personal communication). The page analyzed here was regarded as subtending 50°.
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41. We thank R. Shapley, C. M. Harris, J. C. Letelier, and M. Stryker for valuable discussions about the properties of retinal ganglion cells and D. Troilo, J. C. Letelier, F. A. Miles, and L. Wise for critical comments on this manuscript. Supported by NIH grant EY02727. V.R. was supported by the College Research Scholars program of City College.

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# Localization of Amyloid β Protein Messenger RNA in Brains from Patients with Alzheimer's Disease

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**The distribution of cells containing messenger RNA that encodes amyloid β protein was determined in hippocampi and in various cortical regions from cynomolgus monkeys, normal humans, and patients with Alzheimer's disease by in situ hybridization. Both $^{35}$S-labeled RNA antisense and sense probes to amyloid β protein messenger RNA were used to ensure specific hybridization. Messenger RNA for amyloid β protein was expressed in a subset of neurons in the prefrontal cortex from monkeys, normal humans, and patients with Alzheimer's disease. This messenger RNA was also present in the neurons of all the hippocampal fields from monkeys, normal humans and, although to a lesser extent in cornu ammonis 1, patients with Alzheimer's disease. The distribution of amyloid β protein messenger RNA was similar to that of the neurofibrillary tangles of Alzheimer's disease in some regions, but the messenger RNA was also expressed in other neurons that are not usually involved in the pathology of Alzheimer's disease.**

WE HAVE USED THE COMPLEMENTARY DNA (cDNA) clone λAm4 (*1*) encoding amyloid β protein (*1–4*) as a template to generate $^{35}$S-labeled RNA probes for localization by in situ hybridization of the messenger RNA (mRNA) encoding amyloid β protein in the cerebral cortex and hippocampus of cynomolgus monkeys, normal human subjects, and patients with Alzheimer's disease (AD). We found that, in all cases, the mRNA encoding amyloid β protein was expressed in specific subpopulations of neurons in the neocortex and hippocampus. In some regions, the size and laminar distribution of these neurons were similar to those of the subset of neurons that develop neurofibrillary tangles (NFT) in AD. But the mRNA encoding amyloid β protein was also expressed in the neurons of other regions of the neocortex and hippocampus that are relatively preserved in AD.

The cortical distribution patterns of NFT and neuritic plaques (NP) suggest that certain cortical cell types and their associated circuits are devastated in AD, whereas others are spared (*5–9*). In addition, certain cytoskeletal proteins, as well as the amyloid β protein, have been implicated in NFT and NP formation (*10*). It has been suggested that the fibrillary amyloid deposits that are present in intracellular NFT, extracellular NP, and the cerebral vasculature in AD all arise from the same amyloid β protein (*2, 11, 12*). In addition, this same protein occurs in the NFT and NP in brains of patients with Down syndrome (*11, 13*). The vascular and extracellular amyloid might enter the brain from the circulation (*14*); however, the recent molecular characterization of am-

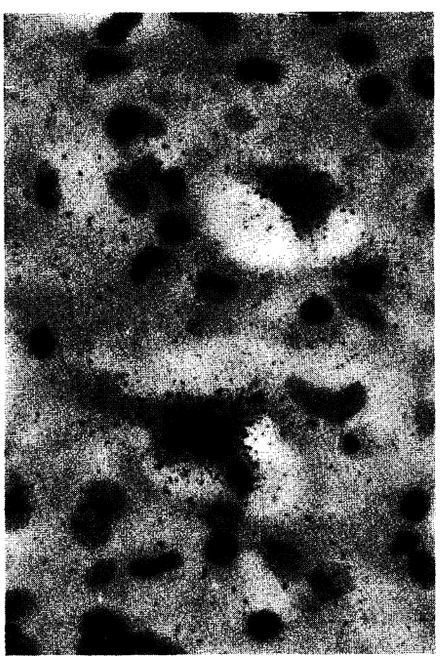

**Fig. 1.** In situ hybridization of amyloid β protein mRNA in the superior frontal gyrus from a patient with Alzheimer's disease (counterstained with cresyl violet and eosin). Note preferential cellular labeling (dark silver grains) on pyramidal cells of layer V.

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