Homeostasis of Eye Growth and the Question of Myopia

Review

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As with other organs, the eye's growth is regulated by homeostatic control mechanisms. Unlike other organs, the eye relies on vision as a principal input to guide growth. In this review, we consider several implications of this visual guidance. First, we compare the regulation of eye growth to that of other organs. Second, we ask how the visual system derives signals that distinguish the blur of an eye too large from one too small. Third, we ask what cascade of chemical signals constitutes this growth control system. Finally, if the match between the length and optics of the eye is under homeostatic control, why do children so commonly develop myopia, and why does the myopia not limit itself? Long-neglected studies may provide an answer to this last question.

Both during development and afterwards, most body parts actively maintain their size and shape, growing or shrinking as necessary. Thus, if one removes part of a rat's liver, the original liver size is restored within days (Michalopoulos and DeFrances, 1997). In salamanders or tobacco plants, if cells are made larger than normal, cell division stops early, resulting in salamanders or leaves that are normal in size and shape (reviewed by Day and Lawrence, 2000). In seasonally breeding birds, the reproductive organs alternate between two sizes during the year (Dawson et al., 2001). Even adult body size can be under homeostatic control: clownfish regulate their body size in proportion to their social status within the group (Figure 1A); if one fish is removed, the fish subordinate to it grows to the size appropriate to its new status (Buston, 2003). A particularly dramatic case of homeostasis is found in those snakes that eat only occasionally. The size of the heart, liver, kidney, and intestine becomes two to three times larger after a meal and shrinks back after the meal is digested (Figure 1B; Secor and Diamond, 1998). In all of these cases, a homeostatic mechanism controls the size and causes dramatic growth changes when necessary.

The eye faces a similar, if less lurid, regulatory challenge. Its length must match the focal length of its optics for images of distant objects to fall on the retina (emmetropia) rather than in front of or behind it. Although this might happen by a perfectly shaped eye in the embryo growing proportionally in all dimensions, this is not what occurs. Instead, vision guides the growth of the eye: if spectacle lenses cause images to fall either behind or in front of the retina (hyperopia or myopia, respectively),

eye growth compensates for the optical effects of the lenses (Figures 1C and 1D; chicks, Schaeffel et al., 1988; Irving et al., 1992; rhesus monkeys, Hung et al., 1995; marmosets, Whatham and Judge, 2001; guinea pigs, McFadden et al., 2004). Fish also show compensation for imposed optical defocus (Kroger and Wagner, 1996).

Emmetropization Compared with Other Systems of Growth Control

In all species studied, the eyes at birth or hatching are ill matched to the focal lengths of their optics. In some, such as macaque monkeys (Smith, 1998) and marmosets (Graham and Judge, 1999; Troilo and Judge, 1993), the eyes are too short and thus are hyperopic; in others, such as ostriches (Ofri et al., 2001) and falcons (Andison et al., 1992), the eyes are too long and thus are myopic; in yet other species, such as humans (reviewed by Curtin, 1985) and chickens (Wallman et al., 1981), some individuals are myopic and others are hyperopic. All grow to emmetropia during the postnatal period. We presume that this homeostatic growth control has two components: active regulation using nonvisual signals that convey size, as is used in the developmental control of other organs, and, specific to the eye, visually guided control of growth. Because emmetropic eyes that are initially of normal size and shape compensate for lenses, thereby becoming abnormal in size and shape, vision must be more powerful than other inputs to the postnatal homeostatic controller.

In other organs in which homeostatic size compensation has been studied, although many of the chemical signals involved are known, the signal that conveys the size information is quite unknown. Thus, it is known that within minutes of removing part of a rat liver the receptors for urokinase plasminogen activator are externalized on the cell surface (Mars et al., 1995), within hours hepatic growth factor is produced, and within days the original liver size is restored through the action of a cascade of growth factors (Michalopoulos and DeFrances, 1997). However, it is not known what signal sets off this cascade, nor what signal terminates it, nor what variable is regulated to maintain the size of the liver.

One theory, now 40 years old, accounts for homeostatic control of organ size by hypothesizing that organs produce a tissue-specific inhibitory substance, a chalone (Bullough, 1965). When the organ is small, the concentration of the chalone is low, but as the organ size increases, so does the chalone concentration, until a point is reached at which the organ size stabilizes. Interest in the chalone concept has been revived by the discovery of a chalone-like inhibitor of muscle growth, myostatin. If the gene for this highly conserved protein is made dysfunctional, increased muscle mass results (Figure 1E; Lee and McPherron, 1999).

There are two modes of homeostasis of organ size. In the case of the liver, regulation is relative to the body size: baboon livers transplanted into humans grow to the size of human livers, and livers from large dogs transplanted into small dogs shrink to the appropriate

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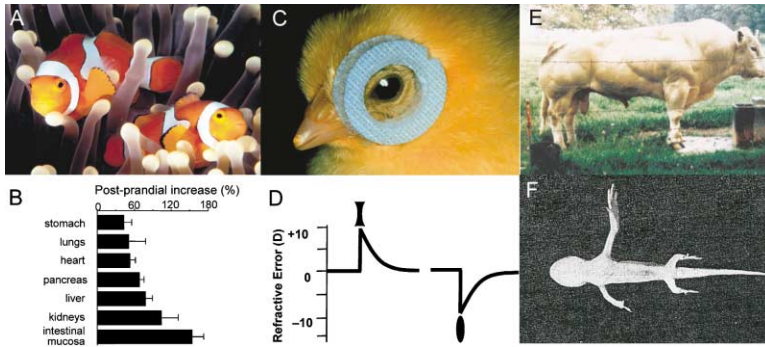
Figure 1. Size Regulation and Homeostasis

The size of body parts (or even whole bodies) is actively regulated. (A) In clownfish, body size is actively regulated so that each fish is 80% the size of the fish above it in social status (Buston, 2003; photo by Dr. Shane Paterson). (B) In snakes that consume large meals infrequently, like pythons, the sizes of many organs are dramatically downregulated during fasting and upregulated after a meal (Secor and Diamond, 1998). (C and D) Visual input can drive changes in eye size and shape, such that a chick eye fit with a defocusing lens will grow faster or slower to eliminate the refractive error and restore focused vision (photo courtesy of C. Wildsoet and K. Schmid). (E) Two breeds of cattle bred for size both have mutations in the myostatin gene (Lee and McPherron, 1999). (F) Embryonic salamander limbs transplanted into embryos of a smaller species develop to their normal size, irrespective of the size of the host (Twitty and Schwind, 1931).

size (Kam et al., 1987). Similarly with the spleen: if multiple fetal spleens are transplanted into a mouse, the aggregate mass of all the spleens equals that of one normal spleen (reviewed by Conlon and Raff, 1999). In these cases, one can suppose that the liver or spleen cells produce a freely circulating inhibitory substance, the concentration of which would drop if the organ were transplanted into a larger animal, leading to an increase in organ size.

Other organs regulate their size autonomously, irrespective of the size of the host. Thus, multiple fetal thymus glands transplanted into a mouse each grow to normal size (reviewed by Conlon and Raff, 1999). Similarly, salamander limbs or eyes transplanted into larger or smaller species of salamanders grow to the normal size of the donor species (Figure 1F; Twitty and Schwind, 1931). The limb and eye differ in that the individual bones of the limb are regulated autonomously, so that in a composite limb made from chick and quail the individual bones retained their species-appropriate size (Iten and Murphy, 1980), whereas an eye made up of parts from salamanders of different sizes was normal in shape and intermediate in size (Harrison, 1929). Regulation independent of body size could be explained by positing that the "chalone" concentration is much higher within the organ than in the body as a whole, so that its concentration rises as the organ grows because the surface-to-volume ratio falls. But whether a chalone-like molecule exists in the eye is quite unknown.

The beauty of studying the homeostatic control of eye growth is that because it is strongly guided by visual error signals, we can manipulate it in ways that would be difficult or impossible with other organs. For example, the set-point about which the eye growth is regulated can be precisely controlled by the power of the imposed spectacle lens, thereby arranging for homeostatic maintenance of different eye sizes. Furthermore, increases and decreases in size can both be studied within a single animal by fitting different spectacle lenses to each eye. Finally, the temporal aspects of the feedback control can be studied by manipulating the timing of the error signals by putting on and off a spectacle lens. Equivalent manipulations would be nearly impossible in the case of the liver or spleen.

Control of Eye Growth by Visual Signals

Spectacle Lens Compensation. The homeostatic control of eye growth functions to keep images sharply focused on the retina. Therefore, if the eye length increases more slowly than does the focal length, the focal plane will be behind the retina, creating hyperopic defocus on the retina. The same occurs if one puts a negative lens over the eye (Figure 2A). To regain sharp focus, the retina needs to be displaced backward to where the image is. This is done in two ways: the eye is lengthened by increasing the rate of growth or of remodeling of the sclera at the posterior pole of the eye (Gentle and McBrien, 1999; Nickla et al., 1997), and the retina is pulled back within the eye by the thinning of the choroid, the vascular layer between the retina and sclera (Figure 2B; Wallman et al., 1995; Wildsoet and Wallman, 1995); once distant images are again focused on the retina (emmetropia), both the rate of ocular elongation and the choroid thickness return to normal.
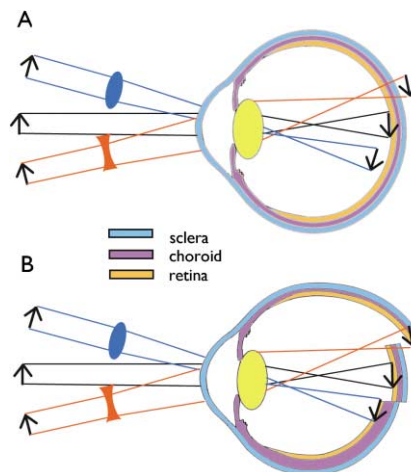

Figure 2. Ocular Compensation for Lens-Induced Defocus

(A) A positive lens (blue, convex) causes the image to form in front of the retina (myopic defocus), whereas a negative lens (red, concave) pushes the image plane behind the retina (hyperopic defocus). With no lens (black rays), the image of a distant object is focused on the retina.

(B) The eye compensates for positive lenses by slowing its rate of elongation and by thickening the choroid, pushing the retina forward toward the image plane. It compensates for negative lenses by increasing the rate of elongation and thinning the choroid, pulling the retina back toward the image plane. The emmetropic eye is intermediate in length and in choroid thickness.
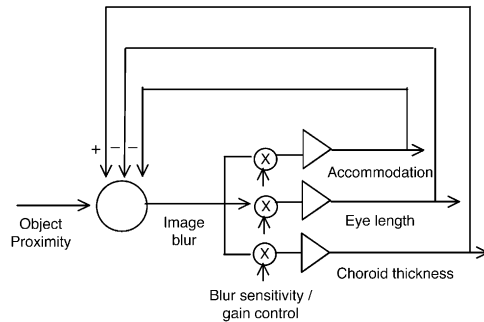
Figure 3. Feedback Control of Refractive Error

Defocused objects induce an error signal (image blur). Three parallel feedback loops each with different time scales can affect this error. For example, increases in accommodation and eye length and decreases in choroid thickness all reduce the blur induced by near objects. The inputs to the three circuits may well be different from one another and may be modulated by adaptation.

Conversely, if the eye length increases more quickly than the focal length does, the image will be formed in front of the retina, creating myopic defocus. The same occurs if one puts a positive lens over the eye (Figure 2A). The eye compensates first by expanding the choroid, which pushes the retina forward toward the image plane, and then by slowing ocular elongation, which causes the continuously increasing focal length of the eye to move the image plane back to the retina (Figure 2B; Hung et al., 2000; Wildsoet and Wallman, 1995).

The range of lens powers compensated for is greater in chicks than in monkeys, although monkeys can also compensate for stronger lenses if the lens power is stepped up gradually (Irving et al., 1992; Smith and Hung, 1999). The greater range of compensation in chicks may be due to the chicks' viewing objects at closer distances (reducing the effective power of the positive lenses), to their visual acuity being lower, and to their amplitude of choroidal compensation being greater (Flitcroft, 1999).

In addition to these changes in eye length and choroid thickness that occur over days or weeks, the eye can change the focal length of its optics in a fraction of second (ocular accommodation). These three processes all act to put the image onto the retina (Figure 3).

Form-Deprivation Myopia. If, instead of being defocused by lenses, the images on the retina are obscured by diffusers or lid suture, eyes elongate and form-deprivation myopia results in all species studied (for example, tree shrew, Sherman et al., 1977; marmoset, Troilo and Judge, 1993; chick, Wallman et al., 1978; rhesus macaque, Wiesel and Raviola, 1977; mice, Schaeffel et al., 2004). Because no images are brought into focus by the excessive ocular elongation, it continues as long as vision is obscured, resulting in eyes whose vitreous chambers are as much as 25% longer than normal (Wallman and Adams, 1987). This dramatic response, conserved widely across taxa, implies that image quality is normally involved in restraining eye growth. When the diffusers are removed, causing the visual system to experience myopic defocus, the choroid thickens, the rate of ocular elongation slows, and the refractions return to normal.

Although both diffusers and negative lenses cause

the eye to be longer and myopic and the choroid to thin, form-deprivation myopia and lens-compensation myopia differ in the time course of scleral biochemical changes (Kee et al., 2001), the effect on the electroretinogram (Fujikado et al., 1997) and on dopamine metabolism (Schaeffel et al., 1995), as well as the effect of optic nerve section (Wildsoet, 2003) and of constant light (Bartmann et al., 1994). Form-deprivation myopia can also be produced in chicks (Nevin et al., 1998), but not monkeys (Smith and Hung, 1999), by excessively strong spectacle lenses of either sign.

Maturity and Homeostasis of Refractive State
Although emmetropization is generally thought of as occurring during early development, homeostatic growth mechanisms need to be at least as precise during maturity if size is to be tightly maintained. Does vision guide eye growth only during a narrow period in development? In tree shrews, there is clear evidence of a period of maximum sensitivity to form deprivation (Siegwart and Norton, 1998). In chicks, however, it appears that susceptibility declines steadily from the earliest period, perhaps being related to the growth rate, with older animals showing consistent but smaller responses to form deprivation (Wallman et al., 1987), even up to 1 year of age (Papastergiou et al., 1998). Adolescent marmosets and rhesus macaques also show decreased, but still significant, form-deprivation myopia (Smith et al., 1999; Troilo et al., 2000b). In humans as well, there is evidence of changes in ocular dimensions in young adults associated with the progression of myopia, perhaps related to visual tasks (McBrien and Adams, 1997). Thus, the young adult eye is still subject to visually guided growth.

Set-Points of Emmetropization
One of the defining attributes of a negative feedback system is its set-point. In the case of the emmetropizing eye, one would expect this set-point to be at emmetropia (distant objects focused on the retina), the refraction that most wild animals and humans who live outdoors achieve (reviewed by Morgan and Rose, 2004, and by Smith, 1998). The experiments on young animals, however, point to each individual having an idiosyncratic set-point, toward which its early growth heads and toward which it returns if its refractive status is offset by defocusing lenses (Smith and Hung, 1999). The set-point is changed if chicks are kept in constant light or have their optic nerves severed, with the eyes again returning to this new refraction when spectacle lenses are imposed (Bartmann et al., 1994; Wildsoet, 2003). Perhaps there are two stages of emmetropization, the first being rapid with individually variable set-points, the second being slower and leading toward absolute emmetropia.

Local Control of Eye Shape
One of the most striking aspects of the effects of both lenses and diffusers on the eye is that they act locally within the eye. If the optic nerve is severed or action potentials in it blocked, form-deprivation myopia is unaffected (Norton et al., 1994; Troilo et al., 1987; Wildsoet and Pettigrew, 1988b), and lens compensation still occurs, although with some differences (Wildsoet, 2003; Wildsoet and Wallman, 1995). Furthermore, if diffusers or negative lenses cover only half of the retina, only that half of the eye becomes enlarged and myopic (Diether and Schaeffel, 1997; Hodos and Kuenzel, 1984; Wallman et al., 1987), and if positive lenses cover half the retina,
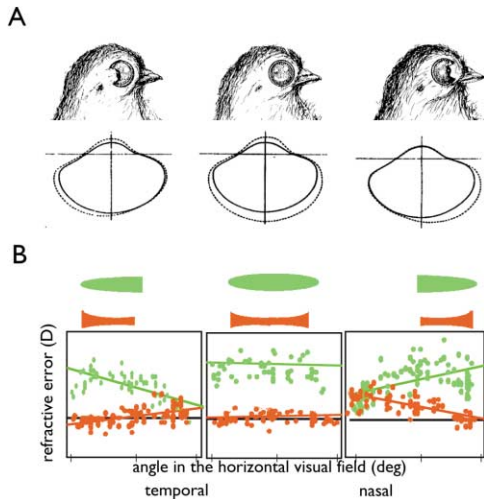
Figure 4. Local Control of Eye Growth and Refractive Error

(A) Eyes form deprived in only the temporal retina (left), nasal retina (right), or over the whole eye (center) have increased length on only the corresponding parts of the retina (dashed lines), relative to the contralateral, untreated eyes (solid lines) (Wallman et al., 1987).

(B) Refractive error of eyes wearing a plus lens (green) or a minus lens (red) as a function of visual angle. If a half-lens defocuses the temporal (left) or nasal (right) retina, local refractive compensation occurs, whereas a full lens induces compensation across the whole eye (middle). Data replotted from Diether and Schaeffel (1997).
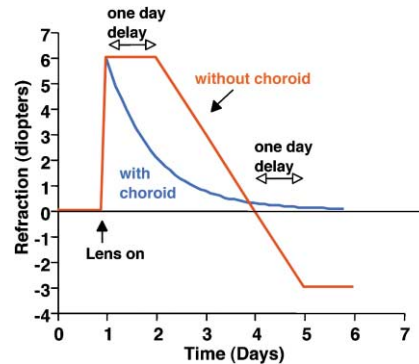

Figure 5. Dynamics of Spectacle-Lens Compensation

In a hypothetical eye without a choroidal response to defocus (red line), a defocusing lens fitted over the eye on day 1 would lead to a delayed compensatory response (day 2). When the eye reached emmetropia (day 4), there would also be a delayed response, leading to an overshoot. In a real eye (blue), the rapid, transient choroidal response prevents overshoot by quickly bringing the eye close to emmetropia.

only that half shows inhibited eye growth (Figure 4). This local modulation of eye shape may be especially prominent in birds because their sclera is rigid and contains a ring of bones, the scleral ossicles (Walls, 1942). Thus, to understand how visual stimuli influence eye growth, we need to consider pathways within the eye from retina to sclera.

In addition, the retinal signals that are modulating eye growth may also act via the brain. Although optic nerve section does not prevent lens compensation, it does affect eye growth (Troilo et al., 1987). Furthermore, in both humans and monkeys, amblyopia, a cortical dysfunction, is associated with hyperopia. Although in the case of children it is difficult to say which is the cause and which the effect, in monkeys made amblyopic by various experimental manipulations, normal emmetropization does not occur (Kiorpes and Wallman, 1995).

If the local growth of the eye is guided by the local refractive error, the arrangement of the external environment might also sculpt the eye. Fitzke et al. (1985) showed that the lower visual field of pigeons is myopic in proportion to the distance from the eye to the ground. (A hint of such a lower-field myopia is seen in humans: Seidemann et al., 2002.) This refractive gradient may partly be driven by the local hyperopic defocus from the ground and partly be a manifestation of the eye's intrinsic shape: chicks raised with a patterned ceiling just above their heads became more myopic in the upper visual field, with a corresponding change in the shape of the eye (Miles and Wallman, 1990). However, there are limits to the extent to which visual inputs can alter the normal shape of the eye in that the peripheral refractions did not match the distance to the ceiling. The

implications of the patterns of peripheral refractions in humans will be discussed at the end of this review.

Dynamic Aspects of Visual Growth Control

In emmetropization, as in any control system, the time course both of the inputs and of the responses are important determinants of performance. To consider the responses first, the eye cannot start and stop growing instantly. In the case of the chick eye, it takes a day or two for the rate of ocular elongation to change after a lens is put on (Kee et al., 2001). As a consequence, if the eye grew at an accelerated rate as long as hyperopic defocus were present, the elongation would continue after it had compensated for the defocus imposed by the lens, causing the eye to become myopic. Such an acceleration of growth toward the end of the growth period could leave the eye permanently myopic. The eye prevents overshooting by thinning the choroid within hours of the lenses being applied, causing the refractive error to be rapidly corrected; this turns off the acceleration of ocular growth, preventing overshoot (Figure 5). This dynamic explanation for the function of choroidal modulation is consistent with the difference in degree of choroidal expansion in different species: chick eyes can grow by 300 μm in 2 days, and the choroid can increase in thickness by this amount; primate eyes grow much more slowly, and the degree of choroidal expansion is much less (Beresford et al., 2001; Hung et al., 2000; Troilo et al., 2000a; Wallman et al., 1995).

The other important dynamic factor is that visual error signals are not constant. Because the degree of myopic or hyperopic defocus fluctuates as one looks about one's surroundings, some objects being in front of the plane of focus and others behind it, the ocular growth control system must integrate these signals over time to infer the refractive state of the eye.

This integration is neither simple nor linear. First, multiple daily episodes of lens-wear result in a much greater growth response in chicks than a single period of the same total duration per day (Winawer and Wallman, 2002). This frequency dependence implies either that the
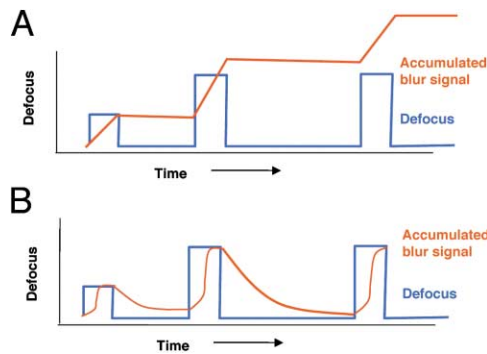
Figure 6. Temporal Integration of Defocus

In a simple linear model of emmetropization (A), the amount of defocus signal accumulated depends only on the total amount of defocus experienced and not on its temporal distribution. In a model more faithful to the data from chicks (B), there is a delay before the signal builds, a saturation after a time, and a decay in the absence of defocus. Thus, the accumulated signal will depend on the frequency and duration of periods of defocus, as well as on the total amount of defocus. The accumulated defocus signal could be neural, biochemical, or a combination of the two.

effect of a given episode saturates after a few minutes or that the signal declines between episodes (Figure 6). Second, if the episodes, however frequent, are each too short (20 s or less), there is little response, implying that some process needs priming before it integrates the visual signal, perhaps analogous to enzymes that require autophosphorylation before they become fully effective.

A third, more provocative, nonlinearity is that when chicks wear positive and negative lenses alternately, each does not cancel out the effect of the other. Instead, the positive lenses dominate, even if the negative lenses are worn for five times as much time as the positive lenses (Winawer and Wallman, 2002). In the extreme case, if negative lenses are worn all day long except for four 2 min episodes of positive lens-wear, the eyes compensate in the direction of the positive lenses (Zhu et al., 2003).

This asymmetry appears to be quite general. If chicks, tree shrews, or monkeys have diffusers or negative lenses removed for an hour each day, the degree of myopia is reduced by at least half (Napper et al., 1997; Schmid and Wildsoet, 1996; Shaikh et al., 1999; Smith et al., 2002). Smith et al. (2002) have shown that the time dependence of this effect is remarkably similar across species (Figure 7). Consider the situation at the end of the experiments: during the hour each day in which the lens or diffuser has been removed, the eye experiences myopic defocus. The effect of this exactly balances the approximately 11 hr of either hyperopic defocus from wearing a negative lens or of form deprivation. Thus, although explicit lens-switching experiments have only been published on chicks, these results strongly suggest that the myopic defocus is more potent than hyperopic defocus in mammals as well. This third nonlinearity may reflect an adaptation to normal patterns of visual experience. For example, if myopic defocus is much rarer than hyperopic defocus in natural environments, emmetropization may require giving it more weight.
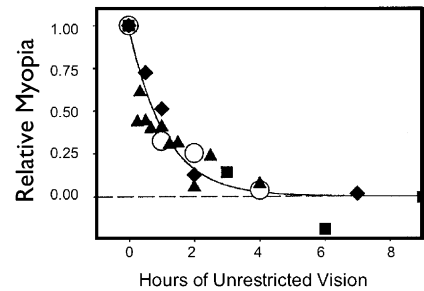

Figure 7. Temporal Characteristics of Myopia across Species

The amount of relative myopia (y axis) as a function of the amount of time each day lenses or diffusers were removed is similar for form deprivation in monkeys (open circles) and chicks (triangles) and negative lenses in chicks (squares) and tree shrews (diamonds). The exponential was fit only to the monkey data. Adapted from Smith et al. (2002).

All three nonlinearities could arise either as a result of neural integrative processes in the retina before an output is produced or as biochemical integration downstream in the choroid or sclera. Truong et al. (2002) have found a visual and a pharmacological manipulation both of which block the ocular elongation to diffusers but only affect the scleral glycosaminoglycan (GAG) synthesis for 2 hr, suggesting that the long-lasting effects of the drug or vision occur at the sclera. This hypothesis requires testing with agents known to affect only the sclera.

How Might the Eye Know Which Way to Grow?
Emmetropization and accommodation face the same challenge: how to discern the sign of the defocus. In principle, there are three ways that the visual system could use blur to direct eye growth to correct myopia or hyperopia. The eye might grow in a random direction and change direction if the blur got worse. Alternatively, the eye could decode the sign of defocus from the image itself. Finally, the eye might be able to achieve emmetropia by elongating in proportion to the magnitude of blur. After a digression on blur, we will discuss each of these possibilities.

What Blur Signal Guides Emmetropization?
The function of emmetropization is to minimize blur. However, blur is not identifiable from the image alone. To take the simplest example, a sinusoidal grating, when defocused, does not change its appearance but only its contrast; one would need to know its in-focus contrast to know whether it is blurred. In viewing a more complex natural scene, one can infer that the image is blurred if the ratio of the amount of low spatial frequencies to high spatial frequencies (that is, in the slope of the power spectrum) is greater than with typical in-focus scenes (Field and Brady, 1997). This method of blur detection would mislead in scenes with atypical distributions of spatial frequencies. Furthermore, it seems obvious that blur is not averaged across regions of the scene, at least for perception and accommodation, as one can accommodate to, or report the sharpness of, individual contours, independent of nearby contours. Therefore, image segmentation must take place in the computation of blur (Field and Brady, 1997). In sum, it is not clear how blur is computed, either for perception, accommo-

dation, or emmetropization. Perhaps different methods are employed by each of these three systems, using the different computational powers available to each. One reason for positing differences among the three is that, although people's eyes can accommodate in the correct direction to a sudden onset of defocus (Fincham, 1951; Smithline, 1974), when asked to clear a target by a manual response, people must resort to trial and error (Stark and Takahashi, 1965). Furthermore, people can accommodate to less blur than they can recognize (Kotulak and Schor, 1986).

However blur is computed, the result may be influenced by adaptation. Several types of adaptation might be involved. At the simplest level, retinal contrast gain control adjusts the contrast sensitivity of retinal neurons up or down if the contrast in the scene is low or high, respectively. Another mechanism, prominent in the early stages of cortical processing, adjusts the sensitivity to particular orientations and spatial frequencies depending on how prevalent particular stimuli are. Thus, viewing a high-contrast grating for a minute will reduce the visual system's sensitivity to gratings of that orientation and spatial frequency (Blakemore and Campbell, 1969). Perhaps by this means the visual system modulates the suprathreshold contrast sensitivity across spatial frequencies, much like the adjustment of an audio amplifier to flatten the spectral response (Georgeson and Sullivan, 1975). Spatial frequency normalization occurs both over a brief time scale, as shown by the enhanced acuity after blurring vision for 30 min (Mon-Williams et al., 1998), and over years, as shown by changes in suprathreshold sensitivity to different spatial frequencies brought about by cataracts or their removal (Fine et al., 2002). In addition to contrast adaptation of spatial frequency channels, there is also an apparently higher level blur normalization, whereby a normal photograph appears to be hypersharp after viewing blurred photographs (Webster et al., 2002), as well as a compensation for the high-order optical aberrations of one's own eye (Artal et al., 2004).

The increase in sensitivity to high spatial frequencies after exposure to blur, as discussed above, manifests itself as an increase in acuity [the high spatial frequency cut-off]. It is a common experience of spectacle wearers that one's acuity improves over minutes after removing one's glasses. This of course does not affect the degree of myopia, which is an optical matter of the eye's focal length relative to its physical length, not a matter of acuity. Some behavioral therapies for myopia [such as the Bates method] may improve acuity by means of neural adaptation without altering the optics of the eye.

The several forms of adaptation just discussed would act to "deblur" images and, thus, would act in parallel with accommodation and emmetropization. Therefore, just as accommodation can reduce the input to emmetropization (if accommodation were perfect, the emmetropization mechanism would never experience hyperopic blur at the fovea), so blur adaptation could reduce the amount of blur at the inputs of either accommodation or emmetropization if the adaptation took place at a level of the visual system earlier than the inputs (Figure 3). If emmetropization principally occurs in the retina, adaptation might not hinder it because retinal contrast gain control is not very specific to spatial frequencies

(Solomon et al., 2004) and thus might only "deblur" the image to a minor extent. In fact, the contrast adaptation signal itself might be used by the retina as a measure of the overall sharpness of the image: chicks wearing spectacle lenses show increased contrast sensitivity, presumably because they experience more blur, and two drugs that interfere with experimentally induced myopia, atropine and reserpine, both increase contrast sensitivity and prevent diffusers from increasing it further (Diether and Schaeffel, 1999).

Unsigned Visual Cues

Trial and Error. Either accommodation or emmetropization could, in principle, determine the direction of defocus by a trial-and-error procedure, much as we focus a microscope. Accommodation appears to be able to respond in the correct direction to a sudden onset of blur (Fincham, 1951; Kruger et al., 1997; for review, see Charman and Heron, 1988). A priori, it would seem less likely that the emmetropization system could find the sign of blur by trial and error because it would require memory of the degree of blur experienced days or months earlier. Although memory would not be required if the rate of change of refractive error were available, as Hung and Ciuffreda (2000) have argued, the rate of change of blur because of emmetropization would be orders of magnitude smaller than would be experienced during accommodation (accommodation, 30 D/s; emmetropization, 4×10^5 D/s, even including the rapid choroidal response). Of course, arguing from plausibility is a dangerous game. Nature has tricks that allow bacteria to use unusual memory mechanisms to tell the direction to a food source in extremely weak gradients (Dahlquist, 2002), a problem with seemingly greater obstacles than those faced by the eye.

Explicit evidence against a trial-and-error mechanism in emmetropization is that chicks given 10 min of lens-wear (followed by a period of darkness) consistently increased choroid thickness after wearing positive but not negative lenses (Park et al., 2001). Because the refractive error does not change in 10 min, these results argue that the eye's initial response to defocus is in the appropriate direction.

Magnitude of Blur. Instead of decoding the sign of defocus at each instant, it might be possible for a young animal to infer the sign of the eye's refractive error from the total quantity, without regard to the sign, of blur it experiences over a period of time. This would be possible if, for example, young animals viewed mostly nearby objects: myopic refractive errors, such as those imposed by positive lenses (or eyes being too long), would then tend to sharpen images, while hyperopic refractive errors (imposed by negative lenses) would tend to degrade images. If defocus signaled the eye to accelerate its elongation and sharp vision signaled it to slow elongation, such a system might regulate refractive error in a manner indistinguishable from a feedback system responding to the sign of the blur (Norton and Siegwart, 1995).

To determine whether the sign or magnitude of blur guides lens compensation, one must distinguish whether positive lenses halt growth because they reduce blur or because they create myopic blur. One study (Schaeffel and Diether, 1999) arranged for positive and negative lenses to both increase the magnitude of blur by a similar
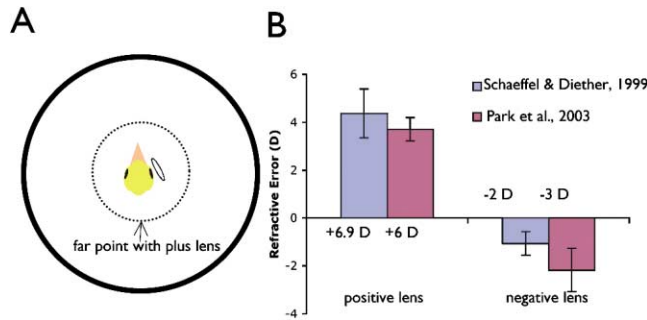
Figure 8. Spectacle Lens-Wear with Restricted Viewing Distance

(A) Chicks were restricted to a central viewing position in a cylinder. For chicks with a positive spectacle lens, the drum wall was beyond the far point (dotted circle) and thus was myopically defocused. With a negative lens, the far drum wall was hyperopically defocused if accommodation was prevented.

(B) Eyes in two studies compensated for lenses of both signs under these conditions.

amount by having chicks wear lenses only when in a restricted environment such that (1) all parts of the visual scene were too far away to be focused while wearing a positive lens, and (2) accommodation was paralyzed to prevent it from reducing the defocus imposed by the negative lens (Figure 8). These chicks compensated in the appropriate directions for negative and positive lenses, as did chicks in a larger study but without cycloplegia (Park et al., 2003). If eyes only responded to the magnitude and not the sign of defocus, they would have responded similarly, not oppositely, to positive and negative lenses in such a situation, as both lenses increased blur.

Moreover, if eyes grew toward myopia whenever blur increased, any manipulation that increased blur should produce an offset toward myopia. If chicks wear lenses composed of negative and positive cylindrical elements with orthogonal axes (Jackson Crossed Cylinders), so that the net spherical power is zero, the amount of blur is greatly increased, but the eyes become slightly hyperopic, not myopic. When such lenses were combined with negative or positive lenses, roughly doubling the amount of blur, the eyes compensated for the negative or positive lenses, ignoring the crossed cylinders, arguing that the sign is not inferred from the magnitude of blur (McLean and Wallman, 2003; Thibos et al., 2001; but see somewhat different results from Schmid and Wildsoet, 1997).

Similarly, when chicks wore weak, image-degrading diffusers superimposed on positive lenses, consistent compensatory hyperopia developed, although myopia developed when the diffusers were worn alone. Indeed, when both eyes wore positive lenses, adding a diffuser to one eye enhanced the lens's inhibitory effect on ocular elongation, despite the poor image quality in that eye (Park et al., 2003). On the other hand, if chicks wore extremely strong positive lenses and were prevented from getting close enough to any objects to bring them into sharp focus, they did not compensate for the lenses (Nevin et al., 1998), suggesting either that sharp vision, rather than myopic defocus, slows eye growth or that the magnitude of the myopic defocus was too great to be compensated. In light of the other results discussed above, the latter seems the more parsimonious explanation.

Analysis of Blur to Determine Sign
The above experiments strongly argue that the eye can infer the sign of the image blur. How might it do this? We will consider several possibilities.

Chromatic Aberration. The most promising cue to de-

focus would be to make use of the longitudinal chromatic aberration of the eye. Because blue light is focused more strongly than red light, if an eye is correctly focused on a black and white edge, the middle-wavelength components of the edge will be in sharp focus on the retina, the blue components will fall in front of the retina, and the red ones behind the retina (Figure 9A). Thus, if the eye is myopic (longer than usual), the red edges will be more in focus than the blue, whereas if it is hyperopic, the reverse will hold. Flitcroft (1990) has shown that the refractive status of the eye can be deduced from the normal output of color-opponent retinal ganglion cells.

Accommodation uses chromatic cues. Fincham (1951) showed that some of his subjects accommodated much more poorly to targets displayed in monochromatic light. Subsequent studies have supported this finding (Kruger et al., 1997). Perhaps the strongest evidence is that, in an open loop setting, many subjects accommodate to a stationary grating chromatically modulated to simulate the effects of a target moving in depth (Figure 9B; Kruger et al., 1995). Furthermore, if a grating stimulates only the short-wavelength-sensitive cones, people tend to overaccommodate, as though the brain knows that in a sharp image the short wavelengths tend to be focused in front of the retina (Rucker and Kruger, 2001).

These findings have led researchers to look for a role of chromatic aberration in emmetropization. Raising animals in monochromatic light does not prevent compensation for spectacle lenses (Rohrer et al., 1992; Schaeffel and Howland, 1991; Wildsoet et al., 1993), demonstrating that chromatic cues are not necessary for spectacle compensation, without resolving whether chromatic cues might be sufficient. The methodological challenge is to isolate the contribution of one cue if several (unknown) cues are employed. This is less of a problem with accommodation in humans in that one can reduce most cues by controlled stimulus presentation. In the lens-compensation experiments just discussed, there were a plethora of other potential cues, as the chicks had many days to freely look at objects at variable distances with intact accommodation. Therefore, whether or not chromatic cues are used, other cues must exist to guide emmetropization.

Nonchromatic Cues. Some subjects can accommodate in monochromatic light even under open loop conditions (eliminating trial-and-error mechanisms) (Fincham, 1951; Kruger et al., 1997), implicating a nonchromatic cue to the sign of blur. Although a perfect optical system would not provide such cues, there are numerous so-
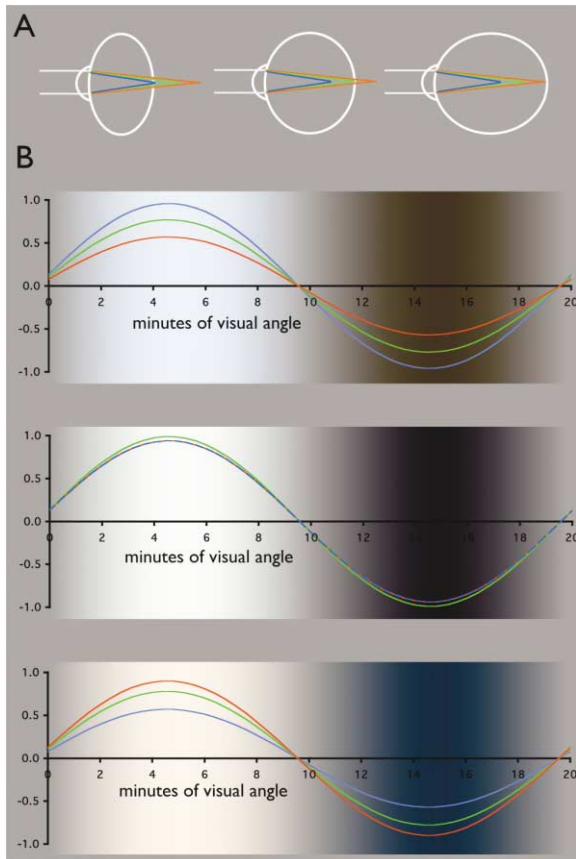
Figure 9. Effects of Longitudinal Chromatic Aberration

(A) Cartoon depicting the multiple planes of focus in a hyperopic (left), emmetropic (middle), and myopic (right) eye. In each case, shorter wavelength light (blue) is focused more strongly than medium (green) or long (red) wavelength light.

(B) The consequences of chromatic aberration on contrast, as indicated by plots of the normalized luminance (y axis) of blue, red, and green light superimposed on a sinusoidal grating. For a hyperopic eye (top), blue light is in best focus and red light in poorest, causing the white region of the grating to have a bluish tint and the black region a reddish tint. The reverse is true for a myopic eye (bottom). For the emmetropic eye (middle), the best focus is closer to green, with both blue and red being defocused. Plots assume a 3 mm pupil and a spatial frequency of three cycles per degree (replotted from Kruger et al., 1995).
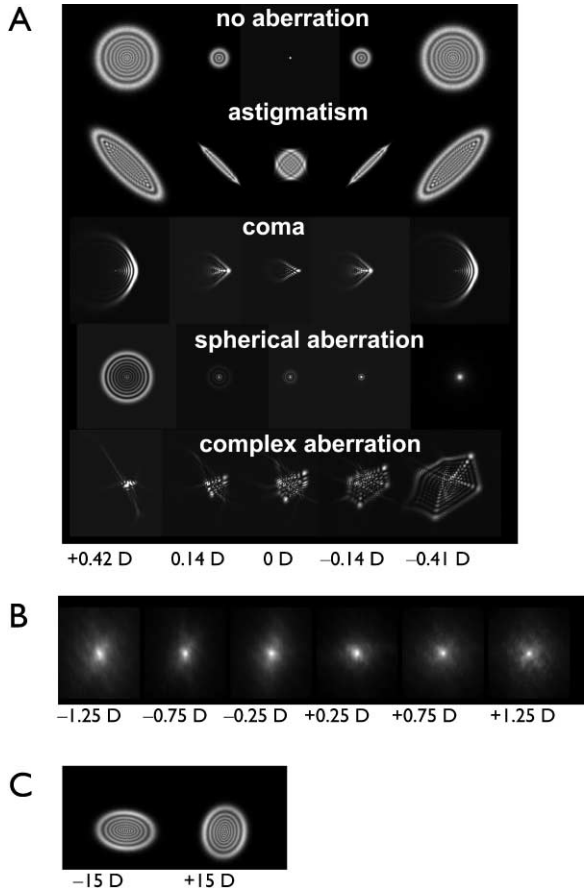

Figure 10. Asymmetries in Point Spread Function with Defocus

(A) Simulations of a single point of light imaged on the retina as a function of defocus. With no aberrations (top panel), the PSF is symmetric with the sign of defocus, but aberrations create asymmetries (panels 2–5) that could be used to infer the sign of defocus. (Simulations by Austin Roorda, University of Houston.)

(B) PSFs from a defocused chick eye. The aberrations make the blur circle on the retina appear different depending on the sign of defocus (Coletta et al., 2003).

(C) Even with massive defocus (±15 D), the effect of astigmatism in a chick eye is asymmetric with the sign of defocus and could provide a cue as to the sign of defocus (Hunter et al., 2003; figure courtesy of Melanie Campbell).

called monochromatic aberrations in the eye, such as astigmatism, spherical aberration, coma, etc., which taken together are not symmetric with respect to the sign of defocus (Figure 10A). These asymmetries are present in the eyes of humans (Woods et al., 1996) and chicks (Figure 10B; Coletta et al., 2003). Indeed human subjects can learn to identify the sign of defocus of images of point sources of light (Wilson et al., 2002). How well these asymmetries could be used with ordinary visual scenes is uncertain. Because these asymmetries cause differences in the modulation transfer function and hence in the contrast sensitivity function of the eye, one could imagine a comparison of different spatial frequencies yielding the sign.

Very recently, Hunter et al. (2003) presented preliminary results showing that the point-spread function of

young chick eyes permitted determination of the sign even with large amounts of defocus (Figure 10C). If confirmed, this finding would confer a theoretical foundation to the findings that chicks appear to be able to discern the sign of defocus.

Accommodation as a Cue. Accommodation could also yield a cue to the sign of the refractive error. The long-term average level of accommodation would indicate whether an eye was hyperopic (much accommodation all the time) or myopic (little accommodation). There is a long history of attempts to link accommodation with myopia in humans, both because it is a prominent feature of near-work and because drugs that block accommodation, such as atropine, reduce myopic progression in children. As we will discuss, accommodation probably has an indirect relation to myopia in humans.

Although we cannot exclude the use of accommoda-

tion in emmetropization, several lines of evidence argue against it being necessary. First, lens compensation persisted after blocking accommodation either by drugs (Schwahn and Schaeffel, 1994), by brain lesion (Schaeffel et al., 1990), or by denervating the ciliary muscle (Wildsoet et al., 1993). Second, lens compensation was also not seriously affected if accommodation was made less effective optically by increasing the eye's depth of focus by imposing blur or image degradation that could not be cleared by accommodation (McLean and Wallman, 2003; Park et al., 2003). Third, emmetropization can occur locally in the retina (Diether and Schaeffel, 1997), whereas accommodation cannot. These results must be viewed with the caveat that accommodation might be used as a cue only for levels of defocus less than that imposed by the spectacle lenses used in these experiments.

Are Accommodation and Emmetropization in Conflict?

How can emmetropization be guided effectively by blur if accommodation nearly eliminates blur? A common view is that emmetropization uses the residual blur left by accommodation. We propose that temporal partitioning might by employed, with accommodation normally acting only briefly and emmetropization ignoring brief intervals of focus or defocus. In fact, very brief periods of lens-wear (20 s or less) do not lead to compensation even if repeated often (Winawer and Wallman, 2002). As we will discuss below, it may be that in humans the act of reading interferes with this temporal partitioning by causing long periods of steady hyperopic defocus, which would not be ignored by emmetropization.

Clues to Visual Cues Employed

Although no single cue has been identified as providing the eye with the direction to grow, one can make three inferences about the nature of possible signals.

First, several cues seem to be employed, complicating the study of emmetropization because negative results from removing a single cue only means that other cues are sufficient. In fact, removing one cue can augment the use of another one. Because the monochromatic aberrations differ at different wavelengths, when chromatic cues are eliminated to test the use of chromatic aberration, this may enhance the use of the monochromatic aberrations.

Second, the cues must be highly resistant to image distortion, as shown by the experiments described in the "Magnitude of Blur" section. This robustness of sign detection might be accomplished by using both the chromatic and achromatic aberrations of the eye.

Third, the compensation for positive and negative lenses appears to have different visual requirements, in that they are blocked by different conditions of flickering light (Schwahn and Schaeffel, 1997) and respond differently to different temporal patterns of lens-wear (Winawer and Wallman, 2002). Furthermore, compensation for negative and positive lenses is differentially affected by drugs that block different populations of retinal neurons (Crewther and Crewther, 2003; Schaeffel et al., 1995; Schmid and Wildsoet, 2004).

Thus, it seems increasingly unlikely that the eye uses a simple trick to grow in the correct direction. Rather,

a combination of cues, probably requiring specialized retinal processing, appears to be involved.

The Sensorimotor Retina and the Visual Signals Controlling Retinal Position

In contrast to the usual view of the retina as the input stage of vision, in the control of eye growth the retina encompasses an entire sensorimotor apparatus. Because lens compensation can occur in eyes with a severed optic nerve, the retina clearly is able both to decode the blur and to move itself forward and backward within the eye by inflating and deflating the choroid and also by controlling the growth of the posterior sclera.

Signal Transmission from Retina to Sclera

How might the retina signal the sclera and choroid to change? Because the control is largely local to the eye, either a retinal chemical signal could act directly on the choroid and sclera or a cascade of signals (one secreted by the retina, another secreted by the retinal pigment epithelium, a third secreted by the choroid) could be involved. We presume that a cascade of signals is involved because it seems unlikely that a retinal signal could penetrate the tight junctions of the retinal pigment epithelium and avoid being washed away in the choroid (which has one of the highest proportional blood flows of any tissue) to reach the sclera.

Although this presumed signal cascade will necessarily pass through the choroid, the signals regulating ocular elongation may be distinct from those regulating choroidal thickness. Evidence supporting this dissociation comes from experiments in chicks in which either the choroidal or the scleral responses to lens-wear were suppressed when vision was limited to brief episodes of lens-wear (Winawer and Wallman, 2002) or when diffusers were worn over plus lenses (Park et al., 2003) or when the daily rhythms were disrupted by repeated light exposures during the night (Kee et al., 2001). On the other hand, we have not found a condition in which the choroid thickens while the eye's rate of elongation increases or vice versa. The dissociability of the choroidal and scleral responses cautions against a simple view of there being a "stop" and a "go" chemical signal controlling emmetropization.

Signaling Cascade: Retina. The retinal beginning of the cascade would most likely be the amacrine cells. Amacrine cells have complex visual responses, they release neurotransmitters and neuromodulators within the retina (ganglion cells, for the most part, do not), and pharmacological treatments that selectively disable amacrine cells have profound effects on eye growth (Barrington et al., 1989; Fischer et al., 1999b; Wildsoet and Pettigrew, 1988a) and block the differential responses to positive and negative lenses (Bitzer and Schaeffel, 2004).

The most studied candidate retinal neuron has been the dopaminergic amacrine cell. Early work showed that form deprivation in both monkey and chick led to decreased dopamine production (Iuvone et al., 1989; Stone et al., 1989). Moreover, giving a dopamine agonist reduced form-deprivation myopia to some extent in monkeys and in chicks (Iuvone et al., 1991; Schmid and Wildsoet, 2004; Stone et al., 1989), and a dopamine antagonist enhanced it (Schaeffel et al., 1995). It has

been proposed that retinal amacrine cells release dopamine, affecting the RPE, which then determines eye growth (Ohngemach et al., 1997). If dopamine were, in fact, the principal retinal output controlling emmetropization, one would expect its concentration to change in opposite directions to positive and negative lenses, a result that has not in general been found (Bartmann et al., 1994; Schaeffel et al., 1995, but see Guo et al., 1995). Furthermore, there is a large difference in the concentration of both apomorphine and reserpine required to block lens compensation in the two directions (Schaeffel et al., 1995; Schmid and Wildsoet, 2004), and when form-deprived eyes have their diffusers removed, the dopamine levels slowly return to normal (Pendrak et al., 1997), whereas the rate of ocular elongation abruptly drops below normal, both findings casting additional doubt on the bidirectional action of dopamine. Finally, complete depletion of dopamine in a fish retina did not prevent the response to either myopic or hyperopic blur, but caused an overall reduction in eye size (Kroger et al., 1999).

The other well-studied candidates are neurons with muscarinic cholinergic receptors. This interest goes back decades to the finding that daily topical treatment of the eye of a child with atropine reduces the rate of myopic progression (Bedrossian, 1979; Kennedy et al., 2000; Shih et al., 1999) and reduces form-deprivation myopia in monkeys (Raviola and Wiesel, 1985), a result long attributed to interference with ocular accommodation. However, the finding that the same occurred in chicks (McBrien et al., 1993; Stone et al., 1991), in which no cycloplegic effect of atropine occurs, and that pirenzepine protects against myopia in chicks and mammals, though it prevents accommodation in neither (Cottriall and McBrien, 1996; Stone et al., 1991), has led attention to the possibility of a retinal site of action.

History has not been kind to this interpretation. First, retinas of chick or tree shrew show no change in acetylcholine concentration as a consequence of form-deprivation myopia (McBrien and Gentle, 2001). Second, retinas in culture experience spreading depression and ERG signs of pathology when treated with muscarinic antagonists at concentrations that block myopia (Schwahn et al., 2000). Third, when retinal cholinergic amacrine cells were destroyed, the eyes remained emmetropic and susceptible to form-deprivation myopia, which could still be blocked by atropine (Fischer et al., 1998b). Fourth, the pattern of effects of different cholinergic antagonists is difficult to reconcile with an action on muscarinic receptors (Luft et al., 2003). Fifth, there are many sites of action of muscarinic agents in the eye, including the RPE, choroid, ciliary body (Fischer et al., 1998a), and likely the sclera (Lind et al., 1998). Thus, although there is no doubt that muscarinic antagonists interfere with myopia in several species, the mode of action is unlikely to be via retinal neurons and may not be via muscarinic receptors. Because both atropine and pirenzepine are currently being used in clinical trials on children, it is urgent to understand their site of action.

The gold standard for relevance to emmetropization is for the concentration of a signaling molecule to change in opposite directions under opposite signs of defocus. Two retinal molecules almost meet this criterion. First, in guinea pigs the level of retinoic acid is increased by negative lenses and reduced by positive lenses (McFadden et al., 2004), and in chicks it is increased by form deprivation (Seko et al., 1998). Furthermore, the levels of mRNA of one of its synthetic enzymes and of the retinoic acid receptor are differentially modulated by lens-wear, and form-deprivation myopia can be reduced by an inhibitor of retinoic acid synthesis (Bitzer et al., 2000).

Second, the glucagonergic amacrine cells show increased expression of the immediate early gene *zenk* by positive lenses and decreased expression by negative lenses (Bitzer and Schaeffel, 2002; Fischer et al., 1999a). In addition, injecting the eye with a glucagon agonist inhibits negative lens compensation, whereas a glucagon antagonist inhibits positive lens compensation (Feldkaemper and Schaeffel, 2002). However, the overall level of retinal glucagon mRNA does not follow this pattern (Buck et al., 2004), perhaps because the regulation is not at the transcriptional level.

Of course, the neural processing of blur almost certainly uses retinal circuits beyond those linked specifically to emmetropization. Therefore, the fact that antagonists to GABA receptors and to nicotinic acetylcholine receptors influence eye growth (Stone et al., 2001, 2003) is subject to several interpretations.

Signaling Cascade: Retinal Pigment Epithelium. Although there is little direct evidence that the RPE is involved in an eye growth signal cascade, several facts provoke interest: dopamine modulates the electrical activity of RPE cells (Gallemore and Steinberg, 1990; Rudolf et al., 1991), RPE cells in culture influence the growth of scleral chondrocytes (Seko et al., 1994), and this effect is strongly modulated by apomorphine, an antagonist of dopamine (Seko et al., 1997). Furthermore, glucagon, which shows a bidirectional modulation with lens-wear, affects RPE cells (Koh and Chader, 1984), as does VIP, another retinal neurotransmitter implicated by some studies of myopia (Seltner and Stell, 1995).

Signaling Cascade: Choroid. In addition to changes in its thickness moving the retina back and forth, the choroid also is part of the signal cascade from retina to sclera. Thus, when sclera taken from an untreated eye is cocultured with choroid from a myopic or hyperopic eye, the rate of scleral proteoglyclan synthesis changes in a direction determined by the donor choroid (Marzani and Wallman, 1997). A plausible mediator of these choroidal effects is retinoic acid.

In chicks the choroid produces large amounts of retinoic acid. This production is differentially affected by lens-wear, in that positive lenses, which inhibit ocular elongation, increase the retinoic acid synthesis more than 2-fold, whereas negative lenses decrease it even more (just the opposite direction of the effects on retinoic acid in the retina). The choroidal retinoic acid is transported to the sclera, where it inhibits proteoglycan synthesis (Mertz and Wallman, 2000). Therefore, it is likely that retinoic acid is a member of the signal cascade modulating eye growth.

The choroid also contains a set of intriguing intrinsic neurons, which might provide a neural path across the choroid (Schrodl et al., 2003).

Motor Outputs
Motor Outputs Controlling Retinal Position: Choroid. The choroid responds to myopic defocus by thickening,
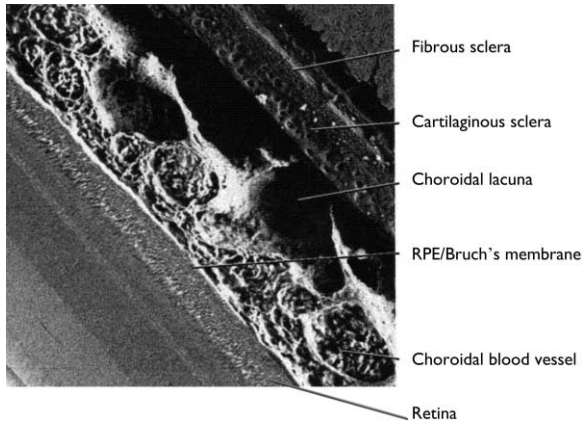
Figure 11. Choroid Thickness and Homeostasis

When the retina detects defocus, it can direct the choroid, the vascular tissue between the retina and the sclera, to inflate or deflate, thereby moving the retina forward or back toward the image plane. Photo from Crewther (2000).

pushing the retina forward toward the image plane, and it responds to hyperopic defocus by thinning, pulling the retina back to the image plane (Figure 2), a mechanism hypothesized by Walls (1942) a half-century before it was demonstrated. Although the thickness changes are most dramatic in the chick, with the choroid quadrupling or halving its thickness in hours or days (Wallman et al., 1995), qualitatively similar changes occur in rhesus monkeys (Hung et al., 2000), marmosets (Troilo et al., 2000a), and tree shrews (Siegwart and Norton, 1998).

In chicks, the increased thickness results mostly through the expansion of the lacunae in the stroma of the choroid (Figure 11; Junghans et al., 1999). The lacunae are membrane-bound spaces that are part of the lymphatic drainage of the eye (De Stefano and Mugnaini, 1997; Junghans et al., 1999; Wallman et al., 1995). The mechanism of the expansion is not known. One possibility is that the synthesis of osmotically active molecules draws water into the lacunae. This is supported by the findings that glycosaminoglycan production in the choroid increases during expansion (Nickla et al., 1997; Wallman et al., 1995), and that, if glycosaminoglycan production is reduced by xyloside treatment, choroidal thickness is also reduced (Rada et al., 2002). Alternatively, choroidal thickness might be regulated via control of fluid transport into and out of the choroid. In support of this possibility, changes in choroidal blood flow precede changes in choroid thickness following form deprivation or recovery (Fitzgerald et al., 2002), and ultrastructural correlates of increased fluid transport into the lymphatic vessels occur during recovery from form-deprivation myopia (Junghans et al., 1999).

In addition to these fluidic mechanisms of modulating choroidal thickness, there are also nonvascular smooth muscle fibers that might provide more rapid thickness modulation (May, 2003; Schrodl et al., 2003; Wallman et al., 1995), especially in young chicks in which the choroidal thinning occurs very rapidly (Kee et al., 2001). Finally, both the vascular and nonvascular smooth muscle of the choroid is innervated by intrinsic neurons of the choroid, which are found in birds and mammals,

including humans, and which synthesize nitric oxide (Schrodl et al., 2003). Perhaps related to this, blocking nitric oxide synthesis immediately inhibits choroidal thickening in response to myopic defocus (Nickla and Wildsoet, 2004).

Motor Outputs Controlling Retinal Position: Sclera. Because the sclera defines the size and shape of the eye, it has been a focus of attention for understanding both emmetropization and the causes of human myopia. Although human myopia was once seen as a scleral defect, in which the thinner scleras of myopic eyes could not resist the normal intraocular pressure, it is now clear that extensive remodeling of the sclera accompanies changes in ocular elongation. Thus, when chick eyes are elongating at a faster rate because of wearing lenses or diffusers, the dry weight of the sclera increases, its degree of hydration decreases and the synthesis of DNA, protein, and proteoglycans increases, whereas the opposite changes occur when elongation is slowed because of myopic defocus (Christensen and Wallman, 1991; Nickla et al., 1992; Rada et al., 1992).

The sclera of most vertebrates consists of two layers: a layer of cartilage and a fibrous layer. Eutherian mammals, as well as snakes and salamanders, have lost the cartilage layer (Walls, 1942), although some molecular signs of it remain (Poole et al., 1982). In chicks, the synthesis of both proteoglycans and DNA are opposite in the two layers: accelerated growth (from wearing negative lenses or diffusers) is associated with increased synthesis in the cartilaginous layer and decreased synthesis in the fibrous layer, whereas decelerated growth (from wearing positive lenses) is associated with the opposite changes (Marzani and Wallman, 1997). (A recent paper [Gentle et al., 2001] did not confirm these changes in the chick fibrous layer, perhaps because these authors labeled the proteoglycans before separating the scleral layers; thus, small amounts of the more intensely labeled cartilaginous layer may have obscured the slight differences in label in the fibrous layer.)

These fibrous and cartilaginous changes in opposite directions are coupled: when cocultured, the fibrous layer from an eye elongating slower or faster than normal can decrease or increase, respectively, the rate of proteoglycan synthesis of the cartilaginous layer from a normal eye (Marzani and Wallman, 1997). Perhaps related to these changes in synthetic activity, when the eye grows toward myopia, the cartilaginous sclera thickens and the fibrous sclera thins (Gottlieb et al., 1990). These thickness changes may result from transdifferentiation of the fibroblasts into chondrocytes during accelerated growth and the reverse during decelerated growth (Kusakari et al., 2001).

Mammalian sclera has only the fibrous layer. When elongation of the eye is accelerated, the sclera reduces its synthesis of extracellular matrix and increases its synthesis of enzymes that degrade the matrix, such as metalloproteinases, resulting in a net loss of tissue (reviewed by McBrien and Gentle, 2003). Similar changes occur in the fibrous layer of the chick sclera (Rada et al., 1999).

The fact that the mammalian sclera thins when the eye elongates more rapidly tempts one to view it as a simple elastic tissue, such that the rate of ocular elongation is governed by the balance between its stiffness

and the intraocular pressure. In support of this view, when strips of sclera from birds or mammals are placed under constant load comparable to that exerted by the intraocular pressure, those from eyes rapidly growing toward myopia elongate ("creep") more than do scleral strips from normal eyes, and tree shrew sclera creeps more than chick sclera (Phillips et al., 2000; Siegwart and Norton, 1999). However, it would be a mistake to view this vision-dependent creep as an in vitro version of the eye's elongation because the rate of creep is several percent per hour, a hundred times the maximal rate of ocular elongation. Furthermore, when the load is exerted by increasing the intraocular pressure in an intact eye, the tree shrew sclera now appears more stiff than the chick sclera, and instead of creeping, it contracts (Phillips and McBrien, 2004). Even more perplexing is the finding in tree shrews that monocular form deprivation and the subsequent recovery from it, which alters the growth rate of only one eye, leads to comparable changes in the levels of collagen-related molecules in both eyes: the mRNA levels of collagen, MMP3 (a metalloproteinase which degrades collagen), and TIMP-1 (an inhibitor of metalloproteinases) all decrease in both eyes during monocular deprivation and all increase when the diffuser is removed (Siegwart and Norton, 2002). Thus, we can only conclude that the sclera is more mysterious than it seems it ought to be and that its mechanical properties change when eye growth changes.

But the sclera is not a simple tissue. In particular, it contains myofibroblasts (Phillips and McBrien, 2004; Poukens et al., 1998), which, in other tissues, contract to resist applied forces. In contrast to the traditional view of the extracellular matrix, in which covalent cross-linking of the collagen molecules provides rigidity and must be broken to permit expansion, dynamic linkages hold the matrix in the shortened state while the myofibroblasts reattach to contract again (reviewed by Tomasek et al., 2002). Scleral myofibroblasts might account for the eye's shrinking, rather than stretching, under elevated intraocular pressure. When tree shrews are treated with a drug that blocks collagen cross-linking, form-deprived eyes elongate more than usual, but the fellow untreated eyes do not (McBrien and Norton, 1994), supporting the view that in normal eyes collagen cross-linking does not provide the only resistance to expansion of the eye by the intraocular pressure. In chicks, the rate of elongation of eyes and the rate of synthesis of glycosaminoglycans (GAG) are normally tightly linked, both changing up or down depending on the visual input. When chicks have proteoglycan production reduced to half by treatment with xylosides, the ocular elongation is reduced by half both in the form-deprived and normal eyes (Rada et al., 2002). However GAG synthesis and ocular elongation can be uncoupled. If form-deprived chicks are given either brief daily periods of vision or are injected daily with pirenzepine, the eyes do not elongate or become myopic, although the glycosaminoglycan synthesis remains elevated, except for brief daily periods (Truong et al., 2002). Furthermore, optical correction of myopia in tree shrews does not reverse the change in scleral GAG synthesis; the myopic phenotype is maintained, although neither the cause of

the myopia nor the myopia itself is present (McBrien et al., 1999).

The normal eye matures from front to back, with the posterior sclera resembling tissue younger than the rest of the sclera. When the eye is elongating toward myopia, the posterior sclera resembles an even younger sclera in that it is more hydrated (chick, Christensen and Wallman, 1991), the creep rate of scleral strips is increased (tree shrew, Siegwart and Norton, 1999), the distribution of collagen fibrils peaks at small diameters (chick, Kusakari et al., 2001; tree shrew, McBrien et al., 2001), and the normal gradient of fibril diameter across the scleral thickness is lost (tree shrew, McBrien et al., 2001). These changes may simply reflect the higher rate of ocular elongation, or they may reflect a reversal of maturation as a means of altering growth.

These findings of strong modulations of scleral growth invite inquiry into the growth factors controlling them. One obvious candidate would be transforming growth factor β (TGF-β), which strongly stimulates GAG synthesis in cartilage (Morales and Roberts, 1988). Unfortunately the several studies of TGF-β on scleral growth (Honda et al., 1996; Rohrer and Stell, 1994; Seko et al., 1995) reached conflicting conclusions. Beyond this, it has been shown that fibroblast growth factor can block form-deprivation myopia in chicks (Rohrer and Stell, 1994), and its receptor (FGFR-1) is upregulated in the sclera of myopic tree shrews (Gentle and McBrien, 2002).

Finally, choroidal retinoic acid is changed bidirectionally with lens-wear, strongly inhibits GAG synthesis (Mertz and Wallman, 2000), and has its receptor upregulated in myopic sclera (Seko et al., 1996), making it likely that retinoic acid plays an important role in controlling scleral growth. In other systems, retinoic acid causes dedifferentiation of chondrocytes (Sandell et al., 1996), as may occur during slowed ocular elongation (Kusakari et al., 2001). How these growth factors interact to regulate scleral growth remains to be worked out.

Are Visually Guided Signals Also Required for Normal Eye Growth? Is eye growth continuously modulated by vision, speeding up and slowing down depending on each momentary visual input, or is there a default growth state of the eye which is perturbed by visual input only when the eye is substantially myopic or hyperopic? If the former, maintaining emmetropization would be the summation of many short periods of modulation by hyperopic and myopic defocus. In this case, any pharmacological manipulation that interfered with compensation for one sign of spectacle lens also would be expected to bias eye growth when no lens was worn. There is some support for this view: at least two drugs which reduce the compensatory response to negative lenses, the muscarinic antagonist pirenzepine and the nicotinic antagonist chlorisondamine, also cause normal eyes to slow growth and become hyperopic (Cottriall and McBrien, 1996; Stone et al., 2001; Truong et al., 2002). Generally, however, the weight of the evidence has supported the view that normal growth is distinct from growth altered by visual manipulations. Atropine reduces myopia in response to lenses or diffusers but does not affect normal eye growth (Schmid and Wildsoet, 2004; Stone et al., 1991). This is true also of apomorphine (Stone et al., 1989), reserpine (Ohngemach

et al., 1997), opiate antagonists (Pickett-Seltner et al., 1997), and basic fibroblast growth factor (Rohrer and Stell, 1994). The lack of effect on normal eye growth argues for normal growth being different from compensation for defocus. Understanding this difference would constitute a major advance in the study of growth mechanisms.

Cyclic Control of Eye Growth. The growing eye elongates mostly during the day. Is this simply a manifestation of the circadian rhythms present in most biological processes, or does it represent a mechanism by which the eye growth is regulated by visual input? Weiss and Schaeffel (1993) first noticed that rapidly elongating form-deprived chick eyes showed a change in this daily rhythm. Nickla et al. (1998) showed that this was a change in phase rather than in amplitude. In elongating chick eyes, the daily rhythms in choroidal thickness and rate of ocular elongation are nearly opposite in phase; when ocular elongation is inhibited by myopic defocus, they shift to being nearly in-phase. A similar phase shift occurs between young, rapidly growing marmoset eyes and older eyes with slowed growth (Nickla et al., 2002). The rhythm of ocular elongation probably results from an intrinsic scleral growth rhythm, in that scleral tissue isolated in tissue culture shows a daily rhythm in the production of GAGs (Nickla et al., 1999).

These correlations raise the possibility that the rate of ocular elongation is determined by the phase relation between the various growth processes (e.g., scleral softening and growth). Perhaps form-deprivation myopia results when synchronization of ocular daily rhythms is weakened because of inadequate signaling of the external light-dark cycle. Consistent with this speculation, making the day-night transition more prominent (30 min of strobe light at dawn and dusk) reduced form-deprivation myopia but not negative lens compensation, whereas manipulations that interfered with the normal circadian cycle (lights on repeatedly at night) reduced lens compensation but not form-deprivation myopia, both pointing to the form-deprived eye being poorly synchronized to the day-night cycle (Kee et al., 2001). Consistent with this interpretation, the reduced synthesis of dopamine in form-deprivation myopia involves only a smaller daily rise in dopamine; the night levels are normal (Stone et al., 1989). We speculate that form vision, in addition to light per se, may function as a synchronizing signal (Zeitgeber).

Human Myopia

It is perhaps obvious that the interest in visual guidance of eye growth is fueled in part by the hope of understanding why myopia is so prevalent among educated people worldwide. We will now consider how the homeostatic control of eye growth relates to the characteristics of human myopia.

As mentioned earlier, most children are born hyperopic or myopic. Over the first few years, their eyes grow to be approximately emmetropic, with least variability at about 6 years of age (Gwiazda et al., 1993a). Over the school years, the prevalence of myopia increases, so that by the end of the university years 25% (United States and Western Europe) to 75% (industrialized countries of Asia) of students are myopic (Saw et al., 1996).

(In addition to the common myopia that develops during the school years or during young adulthood, there is another type of myopia, pathological myopia, that begins earlier, has a clear genetic basis [Young et al., 1998], and is apparently not the consequence of visual experience [Curtin, 1985]. We will not discuss this type further.)

Epidemiological Findings and Possible Association with Near-Work

Until the past decade or two, the conventional wisdom had been that myopia was principally genetic in origin both because of the higher incidence of myopia among the children of myopic parents and the large differences in myopia prevalence among ethnic groups (Mutti et al., 2002). This view was weakened by the discovery of homeostatic control of refractive error in animals, including primates. This gave credibility to the epidemiological evidence accumulating over decades that visual factors might contribute to myopia in humans. The evidence is of three types. First, there are epidemiological studies in many countries showing an association between the educational level attained and the prevalence of myopia (e.g., Goldschmidt, 1968; Sperduto et al., 1983), ranging from 3% for unskilled laborers to 30% for those with university educations. Second, a high proportion of young adults who do intensive professional studies (medical, law, engineering, or pilot school) become myopic over the few years of study (e.g., Kinge et al., 2000; Zadnik and Mutti, 1987). Third, cultures in which people lead outdoor lives have little myopia (Morgan and Rose, 2004), but when compulsory education and the other attributes of modern Western culture were introduced to Inuit or American Indian villages, there was a 4-fold increase in the incidence of myopia within one generation (Bear, 1991), although it is difficult to dissociate the visual changes from dietary and other changes (Cordain et al., 2002). The thrust of these findings is that education is associated with an increased prevalence of myopia. The risk factor most discussed as the intervening variable is reading, because the nearness of the page presents the eye with hyperopic defocus. Although the accommodation system reduces this hyperopic defocus, it cannot eliminate it, because accommodation is under negative feedback control, with defocus being the error signal that drives the accommodation output. Therefore, it is plausible that continuous hyperopic defocus during reading drives the emmetropization mechanism to correct this apparent refractive error by making the eye myopic.

Related to this, there has been a view, which has existed on the margins of science for decades, that most myopia is iatrogenic, in that the eye doctor, instead of letting the myopia stabilize at the level that brings the page into focus, corrects the vision with negative lenses, which reimposes the original error that caused the myopia in the first place (Medina and Fariza, 1993). Needless to say, this idea has not been explicitly tested, as that would require randomly assigning some myopic children to be uncorrected, a procedure unlikely to be tolerated by parents or institutional review boards. A more modest test of this hypothesis was to undercorrect the myopia of children. Several small studies found undercorrection to reduce myopic progression (Goss, 1994; Ong et al., 1999), but in a recent, larger study, undercorrected chil-
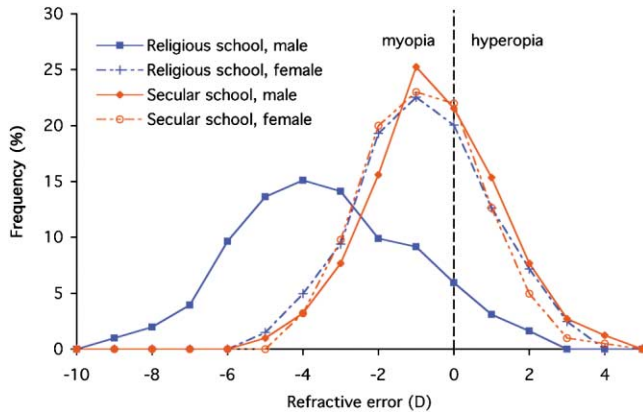
Figure 12. Near-Work and Myopia

Frequency distribution of refractive errors in four populations of Israeli students. Boys in religious schools, who do much sustained near-work, have a much higher prevalence of myopia than do girls in religious schools or than either girls or boys in secular schools (replotted from Zylbermann et al., 1993.)

dren showed greater, not less, myopic progression than those who were fully corrected (Chung et al., 2002).

Within a society, the correlation between the amount of near-work a child does and myopia is much weaker than the epidemiological data just cited. Thus, some studies find a strong association between the hours of near-work and myopia (Richler and Bear, 1980; Saw et al., 2002), whereas other very careful studies find only a weak association (Mutti et al., 2002). It is our view that the daily hours of near-work is not an appropriate measure because of the strongly nonlinear integration of the episodes of lens-wear shown by the animal studies ("Dynamic Aspects of Visual Growth Control" section). If the hyperopic defocus during reading is analogous to negative lens-wear in animals, the duration and frequency of interruptions would be as important as the amount of time spent reading. Measuring near-work in terms of diopter hours (the product of the nearness of the page and the hours of reading) is even less appropriate, in that there is no evidence that the rate of lens compensation depends on the amount of blur beyond a low threshold. Consequently, it is not surprising to us that in many studies only a weak association with myopia is found. Two studies that made use of an unusually large difference in the amount of reading within a group were those of children attending religious schools in Israel, in which the boys read much more than either the girls or the children in secular schools. In this case, only the boys attending religious schools become markedly myopic, an effect unlikely to be due to differences in nutrition or background (Figure 12; Ben-Simon et al., 2004; Zylbermann et al., 1993).

Of course, one cannot disprove the importance of a genetic component by showing the importance of the environment any more than one can do the reverse. Myopia may resemble heart disease or obesity in resulting from a complex interaction between genetics and environment. Studies of twins generally show a significant interaction between genetics and environment (Chen et al., 1985), as well as a high heritability of refractive errors (Hammond et al., 2001). Heritability, however, is not a measure of the relative influence of genetics and environment but of the influence of heredity in a given environment: in populations in which the incidence of myopia is rapidly changing, such as Inuits exposed to education, the heritability of myopia is much lower than in populations with stable myopia (Morgan and

Rose, 2004). The question is to understand which variables are the relevant ones.

Accommodation and Emmetropization

Because both accommodation and emmetropization reduce blur and thus act in parallel, one would expect that the less effective accommodation is, the more myopia might result from near-work because of the presence of greater blur. Evidence in favor of this hypothesis is that myopes tend to have poorer blur-driven accommodative function, especially while the myopia is developing (Abbott et al., 1998; Gwiazda et al., 1995; Jiang and Morse, 1999). Furthermore, a recent large clinical trial of fitting children with progressive addition lenses to test whether this would slow myopic progression (the lenses would reduce the blur during reading) found that those children with weaker accommodation obtained more benefit from wearing these lenses (Gwiazda et al., 2003).

The relation between accommodation and emmetropization is complicated by several factors. First, the amount of blur present during normal viewing may depend as much on convergence accommodation (the accommodation incidental to adjusting the gaze angle of the two eyes) as on blur-driven accommodation. Thus, to infer the amount of blur present, the characteristics of the accommodation and vergence systems and their interconnections must be considered (Flitcroft, 1998; Schor, 1999). Second, even in the absence of input, there is a tonic level of accommodation (Rosenfield et al., 1993). Because blur-driven accommodation is incomplete, the only unblurred images are of objects at the distance corresponding to this tonic level, which differs for myopes and hyperopes (Zadnik et al., 1999).

Third, long periods of near-work leave the eye slightly myopic for a few minutes afterwards (hysteresis of accommodation), which has led to the suggestion that this myopic defocus might lead to myopia (Ciuffreda and Lee, 2002; Ebenholtz, 1983). In light of the work discussed above concerning brief myopic defocus canceling the effects of long periods of hyperopic defocus, we would be inclined to the opposite interpretation, namely that brief myopic defocus after each period of reading would protect the eye against myopia. Thus, it is uncertain whether to attribute the greater duration of this transient myopia in myopic children (Wolffsohn et al., 2003) to being a cause of myopia or a compensatory mechanism resulting from it. The Chinese practice of

having schoolchildren take breaks from studying to do eye exercises might reduce myopic progression by providing brief periods of sharp or myopically defocused vision.

Reading

Reading is the factor most often pointed to as predisposing a child toward myopia. The slight hyperopic blur caused by the nearness of the page—more if accommodation is weak—is posited either to provoke homeostatic compensation or to degrade image quality causing form-deprivation myopia. We propose other relevant effects of reading: most near tasks other than reading present a combination of hyperopic defocus (at the point of regard) and myopic defocus (from objects in the background). Given the extreme potency of myopic defocus in countering the effect of long periods of hyperopic defocus in all animals examined (Figure 7; "Dynamic Aspects of Visual Control" section), most near tasks may not provoke the emmetropization mechanism at all. Reading, however, may lead to myopia because the page occludes most distant objects, and because it involves long continuous periods of near-viewing. Thus, the pattern of bouts of reading may be more important than the total amount of reading.

We speculate that the age at which reading starts may be important. Myopes are reported to read blurred text better than emmetropes (Rosenfield and Abraham-Cohen, 1999). Perhaps children who start reading earlier (as children in Asia are said to do) or who read more might be better at identifying letters and words and thus relax at least the voluntary component of accommodation, leading to more hyperopic blur, which is corrected by the emmetropization system, resulting in myopia. Alternatively, the causal arrow might point the other way: myopic children (if they are not fully corrected) would see distant objects as blurred, thus attenuating high spatial frequencies. This, in turn, may result in their brains boosting the amplification of high spatial frequencies. During reading this "sharper" image would lead to reduced accommodation (if the input to accommodation is after the stage of blur adaptation) and thus more blur, which would spur the emmetropization system to lengthen the eye. Then, once the myopia stabilized (and was corrected), the high-frequency boost would be removed and accommodation would return to normal. This could explain the transient decrease in accommodative gain as myopia is developing (Gwiazda et al., 1995). To understand emmetropization we need to know where in the visual system the signals driving both accommodation and emmetropization are derived.

Optical Aberrations and Human Myopia

The finding that even mild visual deprivation can lead to myopia has led to the hypothesis that any optical aberrations (defocus, astigmatism, or the so-called higher-order aberrations) might predispose an eye to myopia. Alternatively, the presence of aberrations may be the way that the eye decodes the sign of the blur to grow in the appropriate direction. Unfortunately for both of these hypotheses, the evidence is mixed on whether the aberrations differ in myopes and emmetropes (reviewed by Llorente et al., 2004).

A third hypothesis is that several attributes of human myopia may be due to spherical aberration (rays through the center of a lens focusing at a different point than

those through the periphery) causing the point of best focus to depend on the spatial frequency (Jansonius and Kooijman, 1998). For myopes, when the eyes are corrected to emmetropia (high spatial frequencies focused on the retina), the optimum focus for middle frequencies is shifted behind the retina (Radhakrishnan et al., 2004), so that for near objects these frequencies would be in focus, although the high frequencies may not be. This finding might explain why myopes accommodate less to hyperopic defocus (Gwiazda et al., 1993b) and perhaps why they are less sensitive to blurred letters (Rosenfield and Abraham-Cohen, 1999), because both accommodation (Mathews and Kruger, 1994) and reading (Majaj et al., 2002) rely mostly on middle spatial frequencies.

The Peripheral Consequences of Being Myopic

Probably because we humans rely so much on foveal vision, nearly all work on myopia has concerned only foveal refractions. However, 70 years ago, Ferree and Rand (1933) showed that, in the periphery, some human eyes become increasingly myopic and others increasingly hyperopic. More recently, several studies, using four different methods, have shown that myopic eyes are hyperopic in the periphery relative to the center because the eye is differentially elongated on the optic axis, while the reverse applies to hyperopic eyes (Figures 13A and 13B; Logan et al., 2004; Millodot, 1981; Mutti et al., 2000; Rempt et al., 1971; Schmid, 2003; see also review by Stone and Flitcroft, 2004; one additional study did not find myopic eyes to be more hyperopic in the periphery than on the optic axis but did find them to be more hyperopic in the periphery than hyperopic eyes were [Seidemann et al., 2002].) This differential elongation along the optic axis may be augmented by traction of the ciliary muscle pulling the peripheral sclera inward (Mutti et al., 2000); indeed, the relative peripheral hyperopia is increased during accommodation (Walker and Mutti, 2002). These changes in the shape of the globe may not occur in birds because of the stiffening cartilage in their scleras.

If the eye becomes hyperopic in the periphery as it becomes myopic on the optic axis, homeostatic signals from the central retina directing the eye to elongate less would be countered by signals from the peripheral retina directing it to elongate more. Because the density of most neurons is greater in the central retina, one might think that the influence of the periphery would be modest; however, the total area of the central retina is quite small (the area from 30 to 40 degrees from the fovea is six times as great as the area from the fovea to 10 degrees away; the area from 30 to 31 degrees from the fovea is 60 times the area of the 1 degree fovea). Consequently, the number of retinal neurons in the central retina is relatively small. In the cumulative distribution across the retina of two types of neurons, the dopaminergic amacrine cells, which have a relatively flat distribution across the retina, and the parasol ganglion cells, which occur 100 times more frequently in the central than peripheral retina, the effect of area dominates, resulting in many more cells in the periphery (Figure 13C). Thus, if there is spatial summation of signals from the myopic center and from the hyperopic periphery, the peripheral signal will dominate the emmetropization, and the eye will continue to elongate until enough of the
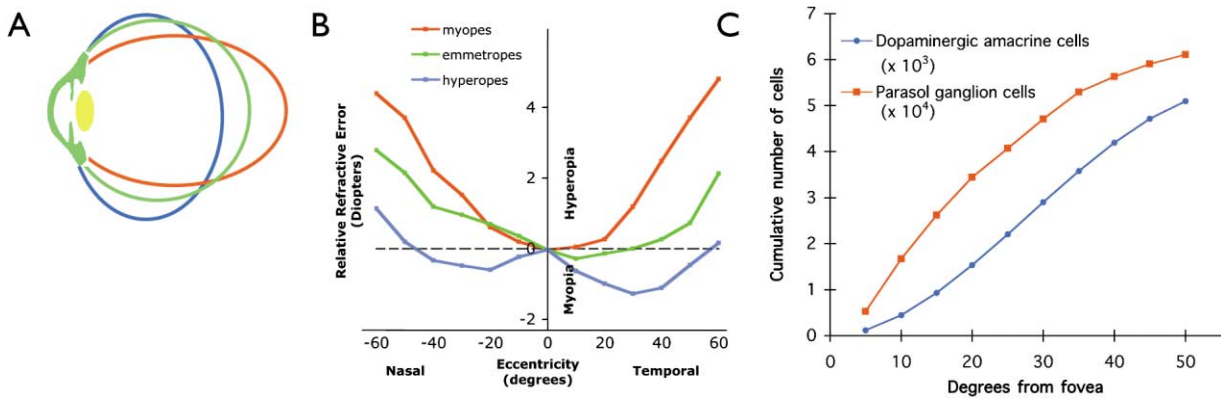
Figure 13. Refractive Errors around the Globe

(A) A cartoon depicting exaggerated differences in eye shape as a function of refractive error. For myopic eyes (red), the posterior elongation results in an prolate globe, which is hyperopic in the periphery, whereas hyperopic eyes (blue) have an oblate shape with myopia in the periphery.
(B) When refractive error is corrected (at the fovea), myopes show a relative hyperopia in the periphery, and hyperopes show a relative myopia (replotted from Millodot, 1981.)
(C) Estimations of the cumulative distribution of two types of retinal neurons as a function of distance from the fovea. Though each type of neuron is densest in the central retina, the central few degrees only makes a small contribution to the total number of neurons summed over a large area (data from Rodieck, 1998).

central retina is myopic that it balances the hyperopic periphery. Correcting the refractions of the central retina (no myopia in center; more hyperopia in periphery) will prevent reaching this balance. In contrast, in hyperopic eyes the peripheral myopia may oppose elongation of the eye, just as imposing myopic defocus does in animals; correcting the hyperopia would make the periphery more myopic and further restrain eye growth (also hypothesized by Seidemann et al., 2002). Indeed, hyperopes tend to stay hyperopic.

It would seem that a better method of correcting myopia is needed. One can envisage that if myopes could wear lenses that corrected not only their central myopia but also their peripheral hyperopia, they would have better vision, and their progressing myopia would be slowed. Progressive spectacle lenses are somewhat like the corrective lenses we are proposing, in that the lower part of the lens would correct the hyperopia in the lower part of the visual field whenever the child was viewing at distance. Therefore, perhaps the efficacy of the progressive lenses, weak as it is, is due to their slight inadvertent effect on peripheral refractions. Lenses with near zones on both the top and bottom of the lens, like the progressive lenses worn by automobile mechanics, might prove to be more effective.

Differences in peripheral refractions may explain why only some children become myopic and why rates of progression vary. Hoogerheide et al. (1971) have shown that, among pilots in training, of those emmetropes and hyperopes who had the peripheral pattern of refractions characteristic of myopes (hyperopic in periphery, low peripheral astigmatism; Rempt et al., 1971), 77% shifted in the myopic direction, compared to 6% of those who had the peripheral pattern characteristic of hyperopia (myopic peripheral refractions) (Figure 14). If these results are confirmed, peripheral refractions would be the best predictor by far of subsequent myopia yet identified.

Conclusions
From the point of view of homeostatic growth control, we have shown that the growth of eyes is guided by

vision and probably by subtle computations on the visual input, in animals as divergent as fish, birds, rodents, and monkeys. Because the visual error signals can be easily manipulated, the homeostatic growth control mechanism of the eye may be decipherable, providing a useful model for the study of size control of other organs.

That eyes control their growth by visual homeostatic mechanisms is shown by the rapid compensation for the defocusing effects of either positive or negative lenses, although the mechanisms and temporal properties of compensation in the two directions are different. For example, briefly wearing a positive lens or removing a
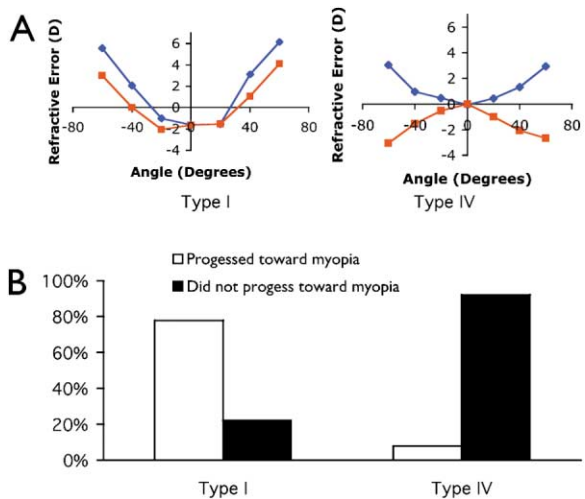

Figure 14. Peripheral Refractive Errors and Myopic Progression

(A) The pattern of peripheral refractions in young adults were classified into five types by Rempt et al., (1971). One type (called type I) was more characteristic of myopes, another (type IV) more typical of hyperopes; refractions along the horizontal meridian (red) and vertical meridian (blue) are shown.
(B) Among pilots in training, emmetropes and hyperopes with type 1 peripheral refractions were much more likely to progress toward myopia than those with type IV (Hoogerheide et al., 1971).

negative lens can cancel day-long wearing of a negative lens in both birds and mammals. The homeostatic controller corrects the defocus by appropriate modulation of the choroidal thickness and of the rate of ocular elongation, although the two can be decoupled to some extent. Visual deprivation also causes myopia, but probably by a different mechanism.

With respect to human myopia, the importance of environmental factors such as educational level argues against viewing human myopia primarily as a genetic disorder or a disease. Instead, the question might be better phrased as: what aspects of ocular homeostasis are associated with myopia? Long periods of reading might defeat the cancellation of blur from distant objects by blur from near ones, and this might drive the set-point in the myopic direction; the temporal pattern of reading may also influence whether myopia develops. Also, accommodation and emmetropization might be weakened by blur adaptation. Finally, the homeostatic control of refractive error appears to be exerted over a broad region of the posterior globe, averaging, for example, myopia in the central retina together with hyperopia in the peripheral retina. Our limiting attention to central vision may prove to have been a myopia in itself.

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