INCREMENTAL RETINAL-DEFOCUS THEORY PREDICTS EXPERIMENTAL EFFECT OF UNDER-CORRECTION ON MYOPIC PROGRESSION

■ George K. Hung, Ph.D.[a]
■ Kenneth J. Ciuffreda, O.D., Ph.D.[b]

a. Dept. of Biomedical Engineering, Rutgers University, Piscataway, NJ.
b. Department of Vision Sciences, State University of New York, State College of Optometry, NY, NY.

ABSTRACT

A recent study[1] found that myopic children who were purposely under-corrected by 0.75D over a two-year period exhibited a small but statistically significant increase in myopic progression as compared to those given full correction. We investigated whether our recently proposed Incremental Retinal-Defocus Theory, which was based on earlier known experimental results, would predict this new finding. Our theory states that any time-integrated reduction in retinal-image defocus area decreases the rate of retinal neuromodulator release. This in turn decreases the rate of proteoglycan synthesis and adversely affects scleral structural integrity, resulting in axial elongation and myopia development. The opposite occurs for an increase in retinal-defocus area. Thus, during an increment of time, a change in defocus due to either ocular growth or imposed optical stimulus provides the directional sense for ocular growth. Analysis of the under-correction condition shows that focusing from far to near represents a change from a large defocus area at a stimulus level beyond optical infinity to a significantly smaller defocus area at the near stimulus level. Thus, repeated far-to-near viewing cycles would result in a cumulative time-integrated decrease in retinal-defocus area that, according to our theory, would increase myopic progression. This is consistent with the experimental findings.

Key Words
accommodation, myopia, refraction, retinal-defocus, vision development

INTRODUCTION

Clarity of the visual image is a vital component of ocular health. A common method for assessing retinal-image clarity is to measure distance visual acuity. The development of a myopic refractive error, however, reduces distance visual acuity, and in turn may adversely impact the quality of ocular health, comfort, and overall quality of life.[2] Yet, the underlying mechanisms that lead to refractive error have remained elusive for centuries. However, recent progress in both experimental and clinical studies has led to the development of the Incremental Retinal-Defocus Theory (IRDT),[3-8] which has provided substantial insights into the underlying mechanisms of refractive error development.

A recent study[1] found that myopic children who were purposely under-corrected by 0.75 D over a 2-year period showed a small but statistically significant increase in myopic progression that was 0.25 D greater than those who were fully corrected. This appears to contradict previous animal studies using high-powered plus lenses that produced relative hyperopic growth.[9] It can be shown, however, that these apparently contradictory findings can be fully explained by an analysis of the accommodative stimulus/response function and application of the IRDT. A schematic analysis will be used to demonstrate systematically the effects in young myopes of: (1) large imposed plus lenses; (2) full correction; and (3) under-correction (as in the Chung et al.[1] clinical trial) on axial growth, and in turn, refractive error development.

BASIC PRINCIPLES OF THE INCREMENTAL RETINAL-DEFOCUS THEORY

The overall mechanism for regulating axial growth rate

In the retina, a center-surround mechanism governs sensitivity to local image contrast, and in turn, the defocus of the retinal-image.[10] Our theory states that an increase in retinal-defocus area (e.g., a change from a small blur circle to a large blur circle) increases surround excitation relative to the center.[5-7] This excitation results in an increase in the rate of neuromodulator-release by amacrine cells, which are sensitive to changes in the surround. A neuromodulator, such as dopamine, transmits this increase via both volume conduction and a cascade of signals through the choroid to the sclera. This in turn results in an increase in proteoglycan synthesis rate, which increases the structural integrity of the sclera. The increased scleral structural integrity retards axial growth rate, thereby resulting in relative hyperopia. Conversely, a decrease in retinal-defocus area has the opposite effect, with a decrease in the rate of neuromodulator release, a decrease in proteoglycan synthesis rate, a decrease in sclera structural integrity, and in turn an increase in axial growth rate. This results in relative myopia (Figure 1). The effects of hyperopic and myopic defocus on the change in retinal-defocus

area following a time increment of genetically pre-programmed ocular growth are shown in Figure 2. Such a change in retinal-defocus area provides the directional sense for ocular growth. Support for our theory can be found in numerous experimental findings discussed below.

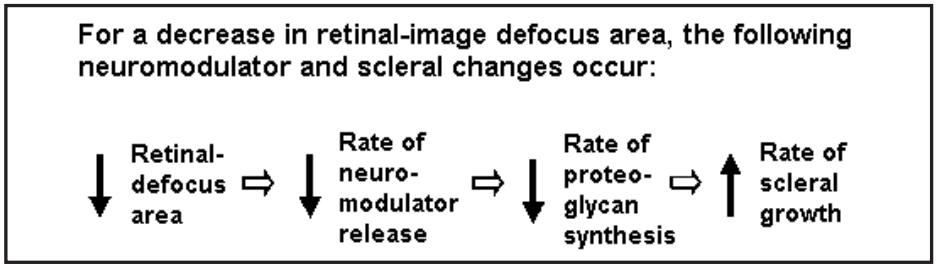


Figure 1. Effect of changes in retinal-image defocus area on scleral growth rate. Based on the Incremental Retinal-Defocus Theory.

Retina as the site for control of axial length growth

Various optically-based manipulations of retinal-image quality have induced specific changes in the axial growth rate.[9,11-16] Moreover, these appropriate changes in growth rate occurred even when the optic nerve was severed[17-19] or the midbrain nuclei for controlling accommodation were lesioned,[20] thus precluding any central or cortical visual feedback mechanism. Hence, the retina is the site for controlling the rate of axial length growth.

Neuromodulators control sensitivity to changes in retinal-image contrast

In contrast to neurotransmitters such as glutamate, acetylcholine, and GABA, which respond rapidly to retinal stimulation, neuromodulators such as dopamine, seratonin, and neuropeptides[12,21,22] act over a longer period, and in addition may cause changes in the neuronal synapses.[23] An example of synaptic plasticity in the retina can be seen in the interplexiform cells in the retina. Experimental results on the teleost retina showed that dopamine is present in interplexiform cells that relay signals from the inner plexiform layer containing amacrine cells to the outer plexiform layer containing horizontal cells, and that the function of dopamine is to modify the effectiveness of the horizontal cells in mediating lateral inhibitory effects in the outer plexiform layer.[22,24] Dopamine serves as a neuromodulator by altering the properties of the horizontal cell membrane and modulating the flow of electrical current across the membrane.[12,21]

The dependence on *change* rather than the absolute level of retinal-image defocus[25] can be regarded as an adaptive mechanism for controlling sensitivity to local contrast. Thus, if an adaptive mechanism can be shown in neuro-modulator control,[26] this would support our proposed mechanism of the dependence on the change rather than absolute level of retinal-image defocus. This is provided by the following excerpt by Dowling:[22]

> *What is the significance of the modulation of lateral inhibition and surround antagonism by dopamine from the interplexiform cells in the retina? Is has long been known that following prolonged periods of time in the dark the antagonistic surround responses of the ganglion cells are reduced in strength or even eliminated. ... interplexiform cells and dopamine play such a role and regulate the strength of lateral inhibition and center-surround antagonism in the retina as a function of adaptive state.*

Moreover, the dependence of the change in retinal-defocus on the most recent level of defocus area is consistent with psychophysical experimental results that showed response adaptation to previously-viewed blur in the retinal image.[27]

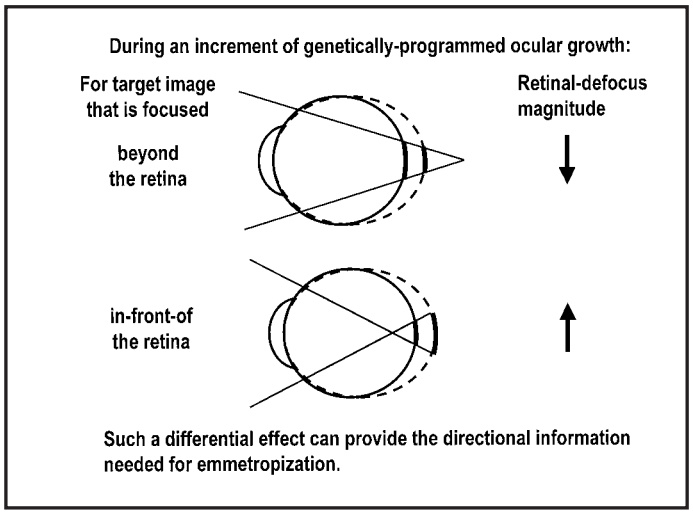


Figure 2. Schematic diagram of the effect of myopic and hyperopic defocus on change in retinal-defocus area following an increment of ocular growth, as shown by the dashed curves.

Cascade of signals from the retina to the sclera

The amacrine and/or interplexiform cells, with their sparse branches in the outer plexiform layer, have been found to operate via volume transmission to influence the other layers of the retina and, in turn, other ocular layers such as the choroid and sclera.[28] In addition, Wallman[29] has pointed out that the retinal pigment epithelium can be a barrier to the diffusion of chemicals, and that the vascular choroid may cause a spreading of the chemicals. Moreover, he proposed that a cascade of signals could traverse through the choroid to reach the sclera. This in turn could control the proteoglycan synthesis rate and consequently the rate of scleral growth.[30,31]

It is important be note that an experimental manipulation which causes changes in retinal-image defocus may take place over minutes or hours, but its final effect on ocular growth may take place over the course of hours to days, or even weeks.

OTHER PROPOSED MECHANISMS FOR THE CONTROL OF AXIAL GROWTH RATE

Other mechanisms have been proposed for determining the appropriate attributes of blur for controlling axial growth. These involve rather complicated processes such as sensing and analyzing chromatic aberration, spherical aberration, spatial gradient of blur or its spatial frequency content (see review by Ciuffreda[32,33]). However, they have not been able to explain satisfactorily the regulation of ocular growth. A more recently proposed mechanism is contrast adaptation.[34-36] Heinrich and Bach[36] found in humans that contrast adaptation occurred for

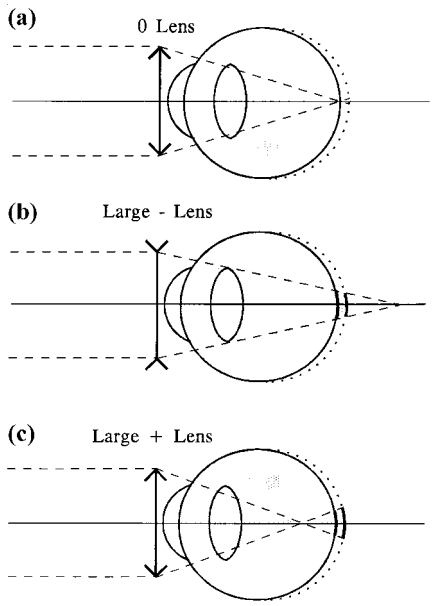
high but not low spatial frequencies, and speculated that this may be a mechanism for discerning between a low contrast stimulus and retinal-image defocus, and in turn emmetropization control. And, Diether et al[34] found in chickens an approximate relationship between change in contrast adaptation and change in refraction after wearing occluders. However, they found no significant difference in contrast adaptation after wearing plus or minus lenses. Moreover, the threshold for significant contrast adaptation effects with intact accommodation was about 4 D of defocus, thus precluding its sensitivity to lower dioptric values of retinal-image defocus as described in the Chung et al.[1] study. Thus, these results on contrast adaptation effects have been mixed.

In addition, since it has been found that choroidal thickness changes occur in the same direction as the related axial length changes,[29] it has been speculated that the choroid might play a major role in myopia development[37,38] rather than only a small to negligible role as suggested by our theory. The resolution of the dilemma is as follows: Although a relationship between changes in retinal-image defocus and choroidal thickness has been noted, the *amount of thickness change was too small* to account for most of the refractive change found.[37,39] Instead, the relationship is more likely the result of neuromodulators, or a cascade of neurochemicals related to the release of the neuromodulators,[24,28,29] passing through the choroid to reach the sclera. The transit of the neuromodulators through the vascular choroid may, as in the case of the monkey, result in a volume change that is observed as a correlated change in choroidal thickness.[37,38,40] However, this change in choroidal thickness would have relatively little direct effect on axial elongation, but rather would provide the medium for the signal cascade from the retina to the sclera as proposed in both our theory as well as that of Wallman.[29]

APPLICATIONS OF OUR THEORY

Lenses

During ocular development, the eye exhibits continuous genetically-programmed growth.[41,42] The effect of the change in retinal-defocus area is different for hyperopic and myopic defocus (Figure 2). The area decreases for hyperopic defocus, but increases for myopic defocus. These changes act to modulate the genetically-predetermined normal growth rate, and thereby alter overall axial length growth rate.[9,11,16]



Below local blur threshold;
Normal rate of neuromodulators;
Normal growth rate.
Dashed lines represent distant light rays. Dotted curves represent growth increments.

Decrease in local blur area;
Decrease in rate of neurotransmitters;
Decrease in rate of proteoglycan synthesis
Increase in axial growth rate relative to normal.

Increase in local blur area;
Increase in rate of neuromodulators;
Increase in rate of proteoglycan synthesis;
Decrease in axial growth rate relative to normal.

Figure 3. Effect of imposed lenses on axial growth rate during an increment of genetically-driven pre-programmed growth.

The imposition of high-powered spherical lenses can cause changes in retinal-defocus area. However, since accommodation *cannot* compensate for the large imposed retinal-defocus area (for large plus and minus lenses), the accommodation system is essentially rendered ineffective. Now, consider the change in area of the blur circle *during a small increment* of normal genetically-programmed ocular growth for large imposed zero, minus and plus-powered spherical lenses (Figures 3a-c, respectively). The illustration is for a point source which is representative of the local effects of the numerous spatially-separated point sources that comprise the viewed target, and together provide the overall effect on ocular growth:

1. When a zero-power lens is imposed, there is *no change* in area of the blur circle. Thus, no additional neuromodulator is released, and the normal genetically-based incremental axial growth pattern of the young eye is maintained.
2. With the introduction of a minus lens, however, the area of the blur circle is *decreased* during the growth increment. Thus, due to the reduction in retinal-defocus area, the rates of neuromodulator release and in turn proteoglycan synthesis are decreased, thereby resulting in a relative increase in axial growth rate.
3. On the other hand, with the introduction of a plus lens, the area of the blur circle is *increased* during the growth increment. Thus, due to the increase in retinal-defocus area, the rates of neuromodulator release and in turn proteoglycan synthesis are increased, thereby resulting in a relative decrease in axial growth rate.

Full Correction

With full correction, the accommodation system *can* compensate for the retinal-defocus changes, and thus operates under the normal closed-loop viewing condition. This can be represented as changes on the well-documented non-linear accommodative stimulus/response function.[32,33,43-51] The accommodative stimulus/response plot has two main response regions: 1) a lead of accommodation (i.e., response above the 1:1 line) at low accommodative stimulus levels so that the accommodative response is greater than the accommodative stimulus, and 2) a lag of accommodation (i.e., response below the 1:1 line) at high accommodative stimulus levels so that the accommodative response is less than the accommodative stimulus with the crossover point occurring at approximately the 1 D stimulus level. The area of retinal-image defocus is equal to the absolute

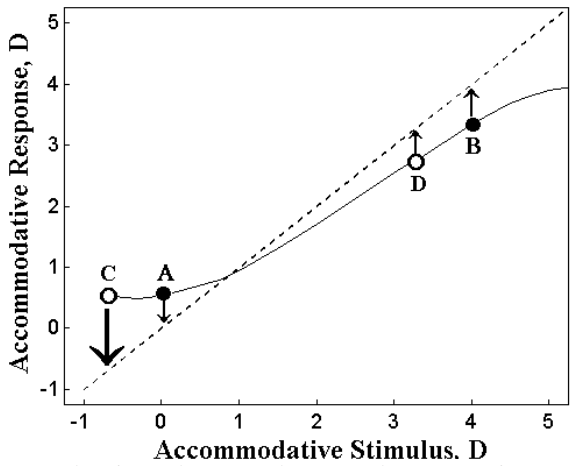


Figure 4. Plot of typical accommodative stimulus-response function. With full correction: A = far response (accommodative stimulus = 0 D), B = response to a target at 25 cm (accommodative stimulus = 4D). With 0.75 D under-corrected vision: C = far response (net accommodative stimulus = 0 - 0.75 D, or - 0.75 D), D = near response to target at 25 cm (net accommodative stimulus = 4 - 0.75, or 3.25 D). Arrow lengths indicate the relative size of the retinal-image defocus area.

value of the difference between the accommodative stimulus and response. Focusing from far-to-near corresponds to a *change* from a specific defocus area at the far stimulus level (~0 D; point A in Figure 4) to a *similar* defocus area at the near stimulus level (point B in Figure 4). Thus, there is relatively little *change* in the area of retinal-image defocus when focusing between these two typical stimulus levels. According to the IRDT this would result in very little if any change in the rate of neuromodulator as well as proteoglycan release, thus resulting in manifestation of only the normal genetically-programmed axial length growth component.

Under-Correction

On the other hand, with a 0.75 D under-correction, as used by Chung et al.,[1] focusing from far-to-near represents a change from a relatively large retinal-defocus area at a stimulus level beyond optical infinity (-0.75 D; point C in Figure 4)[32.33.43-51] to a significantly *smaller* retinal-defocus area at the near stimulus level (point D in Figure 4). Thus, a relatively large *decrease* in retinal-image defocus area would occur.

Our theory can be applied directly to the Chung et al.[1] study with children. Since a young child spends a considerable portion of the day looking at far objects, the -0.75 D stimulus level can be considered their baseline level. Thus, due to the 0.75 D under-correction, non-compensatible retinal-image defocus is produced. Periods of nearwork can be considered as episodes away from this relatively large retinal-defocus area baseline level (point C in Figure 4) to a smaller retinal-defocus area at a higher accommodative stimulus level (point D in Figure 4). Repeated far-to-near viewing cycles would now result in a cumulative time-integrated *decrease* in retinal-defocus area relative to the baseline level. According to the IRDT, this would lead to a decrease in the rates of neuromodulator and proteoglycan release, thereby resulting in increased axial growth rate.

It should also be pointed out that a similar amount of myopic over-correction would shift the effective accommodative stimulus to the right on the AS/R curve. But since the young myopic child would be able to accommodate and thereby compensate for the imposed retinal defocus at both far and near, relatively little effect on retinal-defocus area and, in turn, myopic progression would be expected. Similarly, since a multifocal lens would allow for focusing the target at both near and far, the IRDT would predict relatively little effect on refractive change during ocular growth.

CONCLUSION

The IRDT has provided a simple, consistent and physiologically-realistic mechanism to explain how large imposed high-powered plus lenses, full correction and under-correction in young myopes results in relative hyperopic, emmetropic and myopic axial growth, respectively:

1. With a high-powered plus lens, accommodative feedback is effectively disabled, thus precluding operation along the accommodative stimulus/response curve. The sense of change in retinal-defocus area can only be obtained during an increment of normal genetically-programmed axial growth. The net decrease in retinal-defocus area results in relative hyperopic growth.
2. With full correction, accommodative feedback is *enabled,* thus providing operation along the accommodative stimulus/response curve. The change in the amount of retinal-defocus area now depends on the shift in response position along the curve. The relatively small retinal-image defocus at far and the similarly-sized retinal-image defocus at near constitutes no effective change in retinal-defocus area when shifting focus between these distances, thus resulting only in normal genetically-programmed axial growth being activated.
3. With under-correction, accommodative feedback is also *enabled*, thus providing operation along the accommodative stimulus/response curve. However, the change from relatively large retinal-image defocus at the stimulus level beyond optical infinity to a significantly smaller amount of retinal-image defocus at near constitutes a measurable decrease in retinal-defocus area, thus resulting in relative myopic growth.

These proposed outcomes based on the IRDT theory are consistent with earlier known experimental findings.[9,11,16] They are also in accord with recent clinical trial findings on children by Chung et al.[1] which indicated greater myopic progression with 0.75 D under-correction than with full correction.

Lastly, if one agrees with the notion that retinal defocus is a significant myopigenic factor, then we propose the following scientifically-based lens treatment for myopia, especially in young children. The laboratory investigation of Chung et al.[1] showed that myopic progression was less in the group of young children receiving the full distance refractive correction rather than the partial correction. The model results of the present study confirm the above based on the commonly-held retinal-defocus hypothesis. And, our earlier computer simulation model findings[6] demonstrated that a low-powered near add of +0.50 to +0.75D under binocular-viewing conditions produced the least amount of retinal defocus over a tested lens range of 2.00D. Given the above, we suggest the following: full distance refractive correction in conjunction with a low plus add at near to minimize the level of chronic retinal defocus, and hence myopic progression.

REFERENCES

1. Chung K, Mohidin N, O'Leary D J. Undercorrection of myopia enhances rather than inhibits myopia progression. Vis Res 2002;42:2555-9.
2. Ong E, Ciuffreda KJ. Accommodation, nearwork, and myopia. Santa Ana, CA: Optometric Extension Program Foundation, Inc., 1997:76-96, 177-201.
3. Hung GK. Models of oculomotor control. Singapore: World Scientific 2001:96-102.
4. Hung GK, Ciuffreda KJ. Model of refractive error development. Curr Eye Res 1999; 19:41-52.
5. Hung GK, Ciuffreda KJ. Differential retinal-defocus magnitude during eye growth provides the appropriate direction signal. Med Sci Mon 2000a;6:791-5.
6. Hung GK, Ciuffreda KJ. Quantitative analysis of the effect of near lens addition on accommodation and myopigenesis. Curr Eye Res 2000b;20:293-312.
7. Hung GK, Ciuffreda KJ. A unifying theory of refractive error development. Bull Math Biol 2000c;62:1087-108.
8. Hung GK, Ciuffreda KJ. An incremental retinal-defocus theory of the development of myopia. Comments Theor Biol 2003;8:511-38.
9. Smith EL, Hung LF. The role of optical defocus in regulating refractive development in infant monkeys. Vis Res 1999;39:1415-35.
10. Werblin F. Control of sensitivity of the retina. Sci Am 1973;228:71-9.
11. Schaeffel F, Troilo D, Wallman J, Howland HC. Developing eyes that lack accommodation grow to compensate for imposed defocus. Vis Neurosci 1990;4:177-83.
12. Luvone PM, Tigges M, Stone RA, Lambert S, Laties AM. Effect of apomorphine, a dopamine receptor agonist, on ocular refraction and axial elongation in primate model of myopia. Invest Ophthalmol Vis Sci 1991;32:1674-7.
13. O'Leary DJ, Chung KM, Othman S. Contrast reduction without myopia induction in monkey. Invest Ophthalmol Vis Sci 1992;33(Suppl.):712.
14. Bradley DV, Fernandes A, Lynn M, Tiggs M, Boothe RG. Emmetropization in the rhesus monkey (Macaca mulatta): birth to young adulthood. Invest Ophthalmol Vis Sci 1999;40:214-29.
15. McBrien NA, Gentle, A, Cottriall, C. Optical correction of induced axial myopia in the tree shrew: implications for emmetropization. Optom Vis Sci 1999;76:419-27.
16. Siegwart JT Jr, Norton, TT. Regulation of the mechanical properties of tree shrew sclera by the visual environment. Vis Res 1999;39:387-407.
17. Troilo D, Gottlieb MD, Wallman J. Visual deprivation causes myopia in chicks with optic nerve section. Curr Eye Res 1987;6:993-9.
18. Wildsoet CF, Pettigrew JD. Experimental myopia and anomalous eye growth patterns unaffected by optic nerve section in chickens: Evidence for local control of eye growth. Clin Vis Sci 1988;3:99-107.
19. Li T, Howland H. Modulation of constant light effects on the eye by ciliary ganglionectomy and optic nerve section. Vis Res 2000;40:2249-56.
20. Troilo D. The Visual Control of Eye Growth in Chicks. Ph. D. Dissertation, Faculty of Biology, City University of New York, New York, NY, 1989.
21. Stone RA, Lin T, Laties AM. Retinal dopamine and form-deprivation myopia. Proc Nat Acad Sci 1989:86:704-6.
22. Dowling JE. Retinal processing of vision. In: Greger R, Windhorst U, eds. Comprehensive human physiology: from cellular mechanisms to integration, vol. 1. Berlin: Springer-Verlag, 1996:773-8.
23. Windhorst U. Specific networks of the cerebral cortex: functional organization and plasticity, In: Greger R, Windhorst U, eds. Comprehensive human physiology: from cellular mechanisms to integration, vol. 1. Berlin: Springer-Verlag, 1996:1105-36.
24. Kolb H. How the retina works. Am Sci 2003;91:28-35.
25. Schmid KL, Strang, NC, Wildsoet CF. Imposed retinal image size changes, do they provide a cue to the sign of lens-induced defocus in chick? Optom Vis Sci 1999;76:320-5.
26. Gilmartin B, Bullimore MA, Rosenfield M, Winn B, Owens H. Pharmacological effects on accommodative adaptation. Optom Vis Sci 1992;69:276-82.
27. Webster MA, Georgeson MA, Webster SM. Neural adjustment to image blur. Nat Neurosci 2002;5:839-40.
28. Bjelke B, et al. Dopaminergic transmission in the rat retina: evidence for volume transmission. Chem Neuroanat 1996;12:37-50.
29. Wallman J. Can myopia be prevented? In: 14th biennial research to prevent blindness science writers seminar in ophthalmology, research to prevent blindness. New York: Research to Prevent Blindness, 1997:50-2.
30. Norton TT, Rada JA. Reduced extracellular matrix in mammalian sclera with induced myopia. Vis Res 1995;35:1271-81.
31. Jiang BC, Woessner WM. Increase in axial length is responsible for late-onset myopia. Optom Vis Sci 1996;73:231-4.
32. Ciuffreda KJ. Accommodation and its anomalies. In Charman WN, ed. Vision and visual dysfunction: visual optics and instrumentation, Vol. 1. London: Macmillan, 1991:231-79.
33. Ciuffreda KJ. Accommodation, pupil, and presbyopia. In: Benjamin WJ, ed. Borish's clinical refraction. Philadelphia: W. B. Saunders, 1998:77-120.
34. Diether S, Gekeler F, Schaeffel F. Changes in contrast sensitivity induced by defocus and their possible relations to emmetropization in the chicken. Invest Ophthalmol Vis Sci 2001;42:3072-3079.
35. Baccus SA, Meister M. Fast and slow contrast adaptation in retinal circuitry. Neuron 2002;36:909-19.
36. Heinrich TS, Bach M. Contrast adaptation in retinal and cortical evoked potentials: no adaptation to low spatial frequencies. Vis Neurosci 2002;19:645-50.
37. Troilo D, Nickla DL, Wildsoet CF. Choroidal thickness changes during altered eye growth and refractive state in a primate. Invest Ophthalmol Vis Sci 2000;41:1249-58.
38. Hung LF, Wallman J, Smith EL. Vision-dependent changes in the choroidal thickness of macaque monkeys. Invest Ophthalmol Vis Sci 2000;41:1259-69.
39. Crewther DP. The role of photoreceptors in the control of refractive state, Prog Retinal Eye Res 2000;19:421-57.
40. Wildsoet CF, Wallman J. Choroidal and scleral mechanisms of compensation for spectacle lenses in chicks. Vis Res 1995;35:1175-94.
41. Scammon RE, Armstrong EL. On the growth of the human eyeball and optic nerve. J Comp Neurol 1925;38:165-219.
42. Goss DA, Wickham MG. Retinal-image mediated ocular growth as a mechanism for juvenile onset myopia for emmetropization. Doc Ophthalmol 1995;90:341-75.
43. Alpern M, Kincaid WM, Lubeck MJ. Vergence and accommodation: III. proposed definitions of the AC/A ratios. Am J Ophthalmol 1959;48:41-148.
44. Heath GG. The influence of visual acuity on accommodative responses of the eye. Am J Optom Arch Am Acad Optom 1956;33:513-24.
45. Morgan MJ. Accommodation and its relation to convergence, Am J Optom Arch Am Acad Optom 1944;21:183-95.
46. Charman WN, Tucker J. Accommodation as a function of object form. Am J Optom Physiol Opt 1978;55:84-92.
47. Hung GK, Semmlow JL. Static behavior of accommodation and vergence: computer simulation of an interactive dual-feedback system. IEEE Trans Biomed Engin 1980;27: 439-47.
48. Ciuffreda KJ, Kenyon, RV. Accommodative vergence and accommodation in normals, amblyopes, and strabismics. In: Schor MC, Ciuffreda K.J, eds. Vergence eye movements: basic and clinical aspects. Boston: Butterworths, 1983:101-73.
49. Miege C, Denieul P. Mean response and oscillations of accommodation for various stimulus vergences in relation to accommodation feedback control. Ophthalmic Physiol Opt 1988;8:165-71.
50. Ciuffreda KJ, Hokoda SC, Hung GK, Semmlow JL, Selenow A. Accommodative stimulus/response function in human amblyopia. Doc Ophthalmol 1984;56:303-26.
51. Hung GK. Sensitivity analysis of the stimulus-response function of a static nonlinear accommodation model. IEEE Tran Biomed Engin 1998;45:335-41.

Corresponding author:
George K. Hung, Ph.D.
Dept. of Biomedical Engineering
Rutgers University
617 Bowser Rd.
Piscataway, NJ 08854
shoane@rci.rutgers.edu

Date accepted for publication:
April 15, 2004