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 increased 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 0.75D 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 geneti-
cally pre-programmed ocular growth are
shown in Figure 2. Such a change in reti-
nal-defocus area provides the directional
sense for ocular growth. Support for our
theory can be found in numerous exper-
imental findings discussed below.

**Retina as the site for control of axial length growth**

Various optically-based manipula-
tions of retinal-image quality have in-
duced specific changes in the axial growth
rate.\(^{5,11-16}\) Moreover, these appropriate
changes in growth rate occurred even
when the optic nerve was severed\(^{17-19}\) or
the midbrain nuclei for controlling ac-
commodation were lesioned,\(^{20}\) thus pre-
cluding 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, serotonin, 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 ef-
ccts 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 mem-
brane.\(^{12,21}\)

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 me-
chanism 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 reti-
nal-image defocus. This is provided by
the following excerpt by Dowling:\(^{22}\)

> What is the signifi-
cance of the modu-
lation of lateral inhibition and sur-
round antagonism by dopamine from
the interplexiform cells in the retina?

Is has long been
known that follow-
ing prolonged pe-
riods of time in the
dark the antago-
nistic surround re-
sponses 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 in-
hibition and center-surround antago-
nism 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 psycho-
physical experimental results that showed
response adaptation to previously-viewed
blur in the retinal image.\(^{27}\)

**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 influ-
ence 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 vascu-
lar 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 to note that an experi-
mental manipulation which causes
changes in retinal-image defocus may
take place over minutes or hours, but its fi-
nal 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 pro-
sed for determining the appropriate at-
tributes of blur for controlling axial
growth. These involve rather complicated
processes such as sensing and analyzing
chromatic aberration, spherical aberra-
tion, 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 reg-
ulation of ocular growth. A more recently
proposed mechanism is contrast adapta-
tion.\(^ {34,35}\) Heinrich and Bach\(^ {36}\) found in hu-
mans that contrast adaptation occurred for

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

**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.**
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. 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. 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, it has been speculated that the choroid might play a major role in myopia development 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. Instead, the relationship is more likely the result of neuromodulators, or a cascade of neurochemicals related to the release of the neuromodulators, 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. 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.

**APPLICATIONS OF OUR THEORY**

**Lenses**

During ocular development, the eye exhibits continuous genetically-programmed growth. 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.

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. 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...
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 result 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. They are also in accord with recent clinical trial findings on children by Chung et al. 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 myopicogenic factor, then we propose the following scientifically-based lens treatment for myopia, especially in young children. The laboratory investigation of Chung et al. showed that myopic progression was less in the group of young children receiving the full distance refractive correction than in the group 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 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.
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Corresponding author:
George K. Hung, Ph.D.
Dept. of Biomedical Engineering
Rutgers University
617 Bowser Rd.
Piscataway, NJ 08854
shoane@rci.rutgers.edu
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