

Comments on Theoretical Biology, 8: 511–538, 2003 Copyright © Taylor & Francis Inc. ISSN: 0894-8550 print DOI: 10.1080/08948550390213120

An Incremental Retinal-Defocus Theory of the Development of Myopia

George K. Hung

Department of Biomedical Engineering, Rutgers University, Piscataway, New Jersey, USA

Kenneth J. Ciuffreda

Department of Vision Sciences, State University of New York, State College of Optometry, New York, New York, USA

Previous theories of myopia development involved subtle and complex processes such as the sensing and analyzing of chromatic aberration, spherical aberration, spatial gradient of blur, and spatial frequency content of the retinal image. However, these theories have not been able to explain all the diverse experimental results, which has been accomplished by our newly proposed incremental retinal-defocus theory. Our theory is based on a relatively simple and direct mechanism for the regulation of ocular growth. It states that a time-averaged decrease in retinal-image defocus decreases the rate of release of retinal neuromodulators, which decreases the rate of retinal proteoglycan synthesis, with an associated decrease in scleral structural integrity. This increases the rate of scleral growth, and in turn the eye's axial length, which produces permanent myopia. Schematic analysis of the theory has provided a clear explanation for the eye's ability to grow in the appropriate direction under a wide range of experimental conditions. In addition, the theory has been able to explain how repeated cycles of nearwork-induced transient myopia leads to repeated periods of decrease in retinal-image defocus, whose cumulative effect over an extended period of time also results in an increase in axial growth that produces permanent myopia. Thus, this unifying theory forms the basis for understanding the underlying retinal and scleral mechanisms of myopia development.

Address correspondence to George K. Hung, Department of Biomedical Engineering, Rutgers University, 617 Bowser Road, Piscataway, NJ 08854–0894, USA. E-mail: shoane@rci.rutgers. edu

Keywords: emmetropization, myopia, nearwork-induced transient myopia, ocular axial length, refractive error, retinal defocus

Clarity of the visual image is a vital component of ocular health. A common method for assessing retinal-image clarity is to measure the distance visual acuity. The development of an uncorrected refractive error, however, reduces visual acuity, and in turn may adversely impact ocular health, comfort, and the overall quality of life. Yet the underlying mechanisms that lead to refractive error have remained elusive for centuries. Fortunately, recent progress in both experimental and clinical studies has led to the development of a comprehensive theory that provides substantial insight into the underlying mechanisms of refractive error development.

There are two main types of refractive error: hyperopia and myopia. Hyperopia, or farsightedness, occurs when the combined optical power of the cornea and the unaccommodated crystalline lens is less than that demanded by the axial length of the eye, so that the retinal image is focused beyond the retina [see cross-section drawing of the eye and its components, (Figure 1) (Last 1968); also see a glossary of vision terms in Table 1]. On the other hand, myopia, or nearsightedness, occurs when the total occular power of the eye exceeds that demanded by its axial length, so that the image is focused in



FIGURE 1 Horizontal section of the eye showing the major ocular components for accommodation. Adapted from Last (1968), with permission.

Term	Definition
Accommodation	A change in the optical power of the crystalline lens to minimize retinal defocus and maximize visual resolution/ visual acuity.
Diopter	A unit of optical power equal to the reciprocal of the focal distance in meters. For example, a lens that focuses parallel light rays 0.5m from the lens has an optical power of 2 diopters.
Emmetropia	A (normal) refractive condition in which distant objects are focused on the retina when accommodation in minimally stimulated.
Emmetropization	A change in the rate of axial growth that compensates for and reduces the effect of retinal defocus, usually over a relatively long time interval.
Hyperopia	A refractive condition in which distant objects are focused behind the retina when accommodation is minimally stimulated.
Crystalline lens	The physiological lens inside the eye, which can change optical power to focus for objects at various distances.
Spherical lens	An optical lens of equal power in all meridians placed in front of the eye to compensate for simple refractive errors.
Myopia	A refractive condition in which distant objects are focused in front of the retina when accommodation is minimally stimulated.
Presbyopia	A reduction in accommodative ability occurring normally with age and necessitating a plus lens addition for clear vision at near.
Refractive error	A deviation from the normal refractive condition resulting in either myopia or hyperopia.
Visual acuity	The ability to resolve fine detail. For example, 20/40 visual acuity means the viewer can resolve a target at 20 feet that a "normal observer" can resolve at 40 feet.

TABLE 1Glossary of terms

front of the retina. Thus, for both myopia and hyperopia, there is a mismatch of the ocular components; this is in contrast to emmetropia, in which this match is perfect. For viewing distant objects, younger hyperopes can attain image clarity by means of accommodation, or an increase in crystalline lens power, but at the expense of increased effort along with a reduced effective accommodative range of clear vision. For myopes of any age, however, image clarity at far cannot be attained with increased accommodation, and, in fact, this would further degrade retinal-image clarity. Thus, uncorrected myopia is associated with more immediate concerns of everyday visual function.

Myopia is a worldwide public health concern (Goldschmidt 1968). It affects 25% of the adult population in the United States (Sperduto et al. 1983) and 75% or more of the adult population in Asian countries such as Taiwan (Lin et al. 1996). It can be corrected by optical means, but the estimated annualized cost to consumers in the United States for vision examinations and corrective lenses is \$4.6 billion (Javitt and Chiang 1994). Also, the wearing of spectacles for myopia may restrict one's vocational and avocational options (Mahlman 1982). Surgical techniques to reduce myopia are available, but they are expensive (Grosvenor and Goss 1999) and are not covered by health insurance. Moreover, despite the continual developments and technological improvements over the past 20 years, there are still surgical and postsurgical risks, along with possible side effects such as long-term hazy vision and dry eve (Javitt and Chiang 1994). Furthermore, surgery does not prevent the subsequent development of adult-onset myopia or other agerelated refractive changes such as presbyopia (Javitt and Chiang 1994). For these reasons, the slowing of myopic progression, as well as the prevention of its initial occurrence, has been of considerable interest to clinicians, scientists, and public health officials alike for decades.

To understand the fundamental mechanisms underlying refractive error development, both genetic and environmental factors must be examined (Ong and Ciuffreda 1997; McBrien and Millodot 1986; Gwiazda et al. 1993; Mutti et al. 1996; Jiang and Woessner 1996; Rosenfield and Gilmartin 1998; Grosvenor and Goss 1999). Evidence for genetic influence is supported by the high correlation of refractive errors found in twins (Kimura 1965; Sorsby et al. 1962; Goss et al. 1988), and also the higher prevalence of myopia in children whose parents were also myopic (Gwiazda et al. 1993). On the other hand, evidence for environmental influence comes from the very rapid increase in the prevalence of myopia in Innuit, Japanese, Chinese, and Native Americans over the past 50 years (Young et al. 1969; Alward et al. 1985; Hosaka 1988; Goh and Lam 1994; Lam et al. 1994; Woodruff and Samek 1977), suggesting an association between their progressively greater amount of time spent on nearwork during formal schooling and the higher rates of childhood myopia prevalence and progression (Pässinen et al. 1989; Wu et al. 1999; Zhang et al. 2000). Thus, both genetic and environmental factors are involved in the development of myopia.

Under normal genetic development during infancy, there is an inherent mismatch between the optical power of the cornea/lens and the axial length of the eyeball (Scammon and Armstrong 1925). Yet, as the normal eye matures, the cornea/lens and surrounding ocular tunics begin to develop in concert to provide a relatively precisely focused image on the retina (Bennett and Rabbetts 1989; Grosvenor and Goss 1999). This process is called emmetropization (Yackle and Fitzgerald 1999). Certain critical information is used to coordinate the cornea/lens and axial growth. One of the most

important cues for regulating axial growth is retinal-image defocus (McBrien and Millodot 1986; Ong and Ciuffreda 1997; Wallman 1997; Norton 1999). Cornea/lens growth and its consequent change in optical power will alter retinal-image defocus, but an appropriate change in the axial length growth rate will act to reduce this defocus and in turn restore the balance between these two components. Since the basic growth of the cornea/lens is genetically predetermined (Sorsby et al. 1962; Goss and Erickson 1987; Goss and Jackson 1993; Fledelius and Stubgaard 1986), emmetropization only involves the regulation and modulation of axial length growth (McBrien and Millodot 1986; Ong and Ciuffreda 1997; Wallman 1997; Norton 1999).

Emmetropization also occurs under environmentally induced conditions. This is evident in numerous studies that have attempted to determine the effect of various optically based manipulations of retinal-image quality on induced ocular growth and overall refractive development. The findings have been mixed with respect to the resultant direction of refractive shift. Some manipulations produced a myopic shift. These included prolonged nearwork (Goss and Wickham 1993; Grosvenor and Goss 1999), purposeful undercorrection for myopia (O'Leary et al. 2000; Chung et al. 2002), graded diffusers (Smith and Hung 2000), and black occluder contact lenses (Tigges et al. 1990; Iuvone et al. 1991). On the other hand, other manipulations resulted in a hyperopic shift. These included very strong diffusers (O'Leary et al. 1992; Bradley et al. 1996), crystalline lens removal (Wilson et al. 1987), and initial imposition of graded diffusers (Smith and Hung 2000). Finally, manipulations using plus or minus lenses in the chick (Schaeffel et al. 1990), tree shrew (Norton 1999; Siegwart and Norton 1999), and monkey (Smith and Hung 1999) resulted in either hyperopic or myopic growth, respectively.

The mechanism for the short-term emmetropization process appeared to be relatively simple, since visual feedback related to retinal-image defocus was believed to provide the requisite cortical control signal to regulate both the direction and magnitude of axial growth. However, such appropriate changes in growth rate occurred even when the optic nerve was severed (Troilo et al. 1987; Wildsoet and Pettigrew 1988) or the midbrain nuclei for controlling accommodation were lesioned (Troilo 1989), thus precluding any central or cortical-based visual feedback mechanism. Moreover, since defocus blur per se is an even-error signal (Stark 1968), it lacks the requisite directional sensitivity for controlling axial growth. For these reasons, the controlling mechanism for the short-term emmetropization process, and in turn the long-term development of myopia, has remained elusive and puzzling to both researchers and clinicians alike for decades.

Previous theories that have attempted to describe the underlying mechanism of myopia development involved subtle and complicated processes such as the sensing and analyzing of chromatic aberration, spherical aberration, spatial gradient of blur, or spatial frequency content of the image (see review by Ciuffreda 1991, 1998). But these were not able to explain all of the known experimental results.

In contrast, our recent unifying theory of refractive error development was able to account for all known clinical and laboratory experimental results (Hung and Ciuffreda 1999, 2000a, 2000b, 2000c, 2002). Two fundamental insights underlie our incremental retinal-defocus theory, which for simplicity is herein called "our theory." First, the presence of retinal-defocus has been shown to be critical in the development of environmently induced refractive error (Schaeffel et al. 1990; Norton 1999; Siegwart and Norton 1999; Smith and Hung 1999). Yet retinal defocus is an even-error signal, which provides magnitude but not directional information (i.e., overfocused and underfocused retinal images of equal size are optically indistinguishable). Hence retinal-defocus magnitude information alone is insufficient to produce refractive error in a consistent direction (i.e., either myopia or hyperopia). Second, manipulations of the visual environment are effective in producing and/or modulating refractive error development mainly during the ocular growth and maturational period up to the mid-teens (Goss and Winkler 1983), although this may occur even in early adulthood under extreme-near visual conditions (Adams and McBrien 1992). This demonstrates the importance of a time-dependent element in producing refractive error. However, environmental manipulations over a given time period have been found to be ineffective in mature adults (Goss and Winkler 1983). Hence, the time-dependent factor must also be accompanied by a time window of susceptibility

Although each insight alone is insufficient for a complete theory, when the two insights above are combined, they provide a coherent framework for a unifying bidirectionally sensitive theory of refractive error development. Our theory is based on the concept that the time-integrated effect of *changes* in magnitude of retinal defocus provides the critical information for directional modulation of axial growth rate. The retinal defocus magnitude changes can be produced either by the imposition of fixed spherical lenses during *increments* of genetically programmed axial length growth, or by direct optical manipulation of retinal defocus during the susceptible period. The term *genetically programmed* is used here to describe the normally occurring ocular growth that has been preprogrammed genetically. This should be distinguished from environmentally induced growth resulting from a change in retinal defocus. However, both involve neuromodulator release, with the environmentally induced component acting to modulate the normal genetically programmed release rate.

BASIC PRINCIPLES OF THE THEORY

Neuromodulators Control Sensitivity to Changes in Retinal-Image Contrast

In contrast to neurotransmitters such as glutamate, acetylcholine, and gamma-amino butyric acid (GABA), which respond rapidly to retinal

stimulation (Dowling 1996), neuromodulators such as dopamine, serotonin, and neuropeptides (Stone et al. 1989; Iuvone et al. 1991; Dowling 1996) act over a longer period, and in addition may cause changes in the neuronal synapses (Windhorst 1996). An example of synaptic plasticity in the retina can be seen in the interplexiform cells in the retina (Dowling 1996). These dopamine-containing neurons receive their inputs from the amacrine cells in the inner plexiform layer, and then send their outputs back to the horizontal cells in the outer plexiform layer (Werblin 1973; Kolb 1994, 1981; Dowling 1996). Dopamine serves as a neuromodulator by altering the properties of the horizontal cell membrane and decreasing the flow of electrical current across the membrane (Dowling 1996; Windhorst 1996). Moreover, because of the center-surround structure of the retina, the interplexiform neurons respond in a graded manner to local retinal-image contrast (Werblin 1973; Kolb 1994; Dowling 1996).

We have proposed that feedback regulation provided by the interplexiform neurons from the inner to outer plexiform layers acts to maintain a relatively constant sensitivity to retinal-image contrast, and furthermore that interplexiform neuronal activity leads to a corresponding change in the neuromodulators (Hung and Ciuffreda 2000a, 2000b, 2000c). Such feedback regulation is useful. It precludes the need for a memory mechanism to register and store previous levels of retinal defocus for the purposes of update and comparison, as was recently suggested (Norton 1999). The release of neuromodulators results in synaptic changes in the horizontal cells (Dowling 1996; Windhorst 1996). This in turn alters retinal sensitivity to center-surround input, which helps to shift the steady-state operating level to permit responsivity to transient changes in local retinal-image contrast. Thus, the net rate of release of neuromodulators is *not* dependent on the absolute level of retinal defocus, but rather on the *change* in retinal-defocus magnitude. The release of neuromodulators also causes structural changes in the sclera via modulation of proteoglycan synthesis (Rada et al. 1992; Norton and Rada 1995), wherein an increase in proteoglycan synthesis rate results in greater structural integrity of the sclera and, in turn, a decrease in axial growth rate relative to the normal growth rate. Conversely, a decrease in proteoglyccan synthesis rate results in less structural integrity of the sclera and, in turn, an increase in axial growth rate relative to normal (Gottlieb et al. 1990; McBrien et al. 1999; Wildsoet 1998; Christiansen and Wallman 1991; Marzani and Wallman 1997; Siegwart and Norton 1999; Troilo, Nickla & Wildsoet 2000).

The Overall Mechanism for Regulating the Rate of Axial Length Growth

Genetically programmed mechanisms determine a baseline rate of neuromodulator release that is associated with normal axial growth rate. Retinal-defocusinduced changes in the rate of neuromodulator release are superimposed onto this baseline rate to modulate the underlying activity level. The net effect of the local-retinal mechanism, as discussed earlier, is that the change in retinal-defocus magnitude, and in turn the change in the rate of neuromodulator release, are in opposite directions with respect to the change in the rate of defocus-induced axial growth relative to normal. Thus, during an increment of genetically programmed ocular growth, a change in retinal-defocus magnitude due to the incremental change in ocular geometry provides sufficient directional information to modulate the rates of release of neuromodulators and proteoglycan synthesis, which in turn produce structural changes in the sclera for appropriate regulation of ocular growth and refractive change (Siegwart and Norton 1999; Wildsoet 1998). For example, during an increment of genetically programmed ocular growth (over days or weeks), if the retinal-defocus magnitude decreases, the axial growth rate increases. This results in relative myopic growth. On the other hand, if the retinal-defocus magnitude increases, the axial growth rate decreases. This results in relative hyperopic growth. These axial growth rate changes are consistent with the emmetropization process.

APPLICATIONS OF THE THEORY

This theory was tested schematically under five critical experimentally based conditions (lenses, graded diffusers, black occluder, very strong diffuser or removal of the crystalline lens, and transient hyperopia) (Hung and Ciuffreda 2000c; 2002). The results showed that our theory was able to explain all known experimental findings. For simplicity but a without loss of generality, only the lens condition is presented in this article. Following this example, our theory is examined in detail under the condition of prolonged nearwork and the effect of nearwork-induced transient myopia. Moreover, a block diagram model is presented and simulated to demonstrate quantitatively the effect of prolonged nearwork on the change in retinal defocus, and, in turn, an increase in axial growth rate.

Lenses

During ocular development, the eye exhibits continuous, genetically programmed growth (Hung and Ciuffreda 1999, 2000a–c). The imposition of a spherical lens causes changes in retinal defocus, which acts to modulate the genetically predetermined normal growth rate, and thereby alter overall axial length growth rate. This modulation can be illustrated by the following example. Consider the effect of introducing spherical lenses in front of the eye. The change in size of the blur circle *during a small increment* of normal genetically programmed ocular growth for large imposed zero-, minus-, and plus-powered lenses is shown schematically in Figure 2, a, b, and c, respectively. A neuromodulator, such as dopamine, maintains a specific



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 magnitude; Decrease in rate of neurotransmitters; Decrease in rate of proteoglycan synthesis; Increase in axial growth rate relative to normal.

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

FIGURE 2 Change in retinal defocus during increment of normal genetically-driven axial length growth for different imposed spherical lenses. Reprinted from Hung and Ciuffreda (2000c), with permission.

level of neuronal activity related to retinal-image contrast by means of the local retinal feedback mechanism as described earlier. The net effect is that the rate of neuromodulator release is dependent not on the absolute level of retinal-defocus magnitude, but rather on the change in retinal-defocus magnitude during the increment of genetically programmed ocular growth. For example, when a zero-power lens is imposed, there is no change in size of the retinal blur circle. Thus, no additional neuromodulator is released, and the normal genetically based incremental axial growth pattern of the young eye is maintained. With the introduction of a minus lens, however, the size of the blur circle is decreased during the growth increment; thus, the rates of neuromodulator release and in turn proteoglycan synthesis are decreased, thereby resulting in a relative increase in axial growth rate (Norton 1999). On the other hand, with the introduction of a plus lens, the size of the blur circle is increased during the growth increment; thus, the rates of neuromodulator release and in turn proteoglycan synthesis are increased, thereby resulting in a relative decrease in axial growth rate (Norton 1999). Hence, either a decrease or increase in mean retinal-defocus magnitude *during* an increment of genetically programmed axial growth is proposed to cause a change in the rate of neuromodulator release, leading eventually to biochemically mediated structural changes in the sclera (Siegwart and Norton 1999; Wildsoet 1998) that are manifest as appropriate changes in the rate of axial growth, which are reflective of the active emmetropization process.

Prolonged Nearwork

Our theory can be applied to the condition of prolonged nearwork, as in the case of the development of school myopia, wherein relatively small amounts of retinal defocus are present over extended periods of time (i.e., weeks or months during the normal school years) (Ong and Ciuffreda 1995, 1997). This can be understood in terms of the interactions between two response measures: the dynamic nearwork-induced transient myopia and the static accommodative stimulus/response function (Ciuffreda 1991, 1998; Ciuffreda and Kenyon 1983; Ong et al. 1993; Hung 1998) (Figure 3). Nearwork-induced transient myopia refers to the transitory myopic refractive shift found with distance viewing immediately following sustained near-



FIGURE 3 Accommodative stimulus/response function showing (point A) the nominal accommodative stimulus condition and lag of accommodation, and (point B) the change in effective stimulus and resultant lag of accommodation following the cumulative effect of repeated nearwork-induced transient myopia. Data represent mean accommodative stimulus-response values for 10 visually normal subjects. Symbols: •, group mean accommodative response; error bars, \pm SEM; \blacksquare , initial pretask refractive state at distance; \Box , initial posttask nearwork-induced transient myopia. Adapted from Ong et al. (1993) with permission.

work (Ong and Ciuffreda 1995, 1997). It is measured as the difference between posttask (\Box in Figure 3) and pretask (\blacksquare in Figure 3) steady-state accommodative response levels at distance. The accommodative stimulus/response function is a static S-shaped curve that exhibits slight overaccommodation at distance and progressive underaccommodation at near with increased dioptric demand (Ciuffreda 1991, 1998).

During nearwork, the accommodative response is typically less than (or "lags") the accommodative stimulus (Figure 3, point A; Figure 4a). However, immediately following nearwork and returning to distance viewing, the accommodative response typically exceeds the accommodative stimulus (i.e., the far point of accommodation is shifted inward) more than usual due to the presence of superimposed nearwork-induced transient myopia and its relatively slow decay back to the initial pretask distance refractive state (Ciuffreda and Wallis 1998) (Figures 3 and 4b). This relatively slowly decaying transitory myopia can be conceptually regarded as placing an equivalent low-powered plus lens in front of the eye (Figure 4c), with the transient myopia remaining for a period of time after near viewing. For example, in normal asymptomatic young adults, nearwork-induced transient myopia takes 30–60s to decay fully (Ong and Ciuffreda 1995, 1997), whereas



Nearwork results in lag of accommodative response and associated hyperopic defocus (pt. A in accommodative stimulus/response curve in Fig. 3). Dashed lines represent light rays from object.

Subsequent viewing at far results in a small transient myopia (nearwork-induced transient myopia).

Plus lens represents equivalent amount of residual transient myopia. Far-to-near carryover of nearwork-induced transient myopia due to slow decay of crystalline lens power can be represented by an equivalent plus lens. Thus, when returning to nearwork, the effective accommodative stimulus is reduced slightly, and the accommodative response is also reduced (i.e., moved down from A to B in the accommodative stimulus/response curve in Fig. 3), resulting in a slight decrease in accommodative error, or retinal defocus.

FIGURE 4 Effect of incompletely decayed nearwork-induced transient myopia on lag of accommodation at near following far viewing.

in symptomatic young adults complaining of blur at far following sustained nearwork, it can last several minutes (Ong and Ciuffreda 1995, 1997); in some very young normal children ages 4 to 9 years, it can also last several minutes (e.g., at least 2 min) (Ciuffreda and Thunyalukull 1999; Wolffsohn et al. 2003). Moreover, the nearwork-induced transient myopia paradigm as it applies to nearwork tasks is not a single event, but rather a series of repeated near-far-near cyclic responses, with the time period for nearviewing being much greater than that for far-viewing. Thus, any incompletely decayed transient myopia during the brief period of far viewing will be carried over to the subsequent period of near viewing. This is the critical factor.

Over many cycles, the cumulative result has the effect of a small plus lens being added during the relatively long periods of near viewing. This reduces the net near accommodative stimulus, and thus shifts the operating accommodative focus point downward on the accommodative stimulus/response function as described earlier. Thus, the net accommodative stimulus is slightly less (by approximately 0.25 to 0.50 diopters, than the initial starting point of 4 diopters (point B in Figure 3) (Ong and Ciuffreda 1997). The result of this net-reduced accommodative stimulus is a slightly reduced accommodative response, and thereby a smaller accommodative error is present. Therefore, the cumulative effect of such repeated, incompletely decayed nearwork-induced transient myopia episodes results in repeated transient decreases in retinal defocus at near. By our earlier arguments as per our theory, this results in a decrease in the net rate of release of neuromodulators, a decrease in proteoglycan synthesis, and in turn an increase in the rate of axial growth relative to the genetically programmed normal amount, thereby producing relative myopic growth.

The preceding principles underlie the progressive development of myopia due to repeated cycles of nearwork-induced transient myopia that is seen in the daily lives of very young children, teenagers, and young adults. This myopigenic effect is even greater in patients with abnormal nearwork-induced transient myopia and related symptoms of blur at distance following nearwork (Ong and Ciuffreda 1997; Ciuffreda and Ordonez 1995). These effects were quantified using our retinal-defocus-based model (Hung and Ciuffreda 2000b, 2000c, 2002) to demonstrate the cumulative and progressive effects of repeated nearwork-induced transient myopia on scleral growth, as described next.

MODEL SIMULATION

To quantify the cumulative effect of repeated nearwork-induced transient myopia on retinal defocus, and the consequent retinal and scleral changes as per our theory that lead to the development of permanent axial-based myopia, a homeomorphic model of the local retinal circuitry was constructed using a simulation software package. The MATLAB (5.3)/SIMULINK (3.0) simulation software package provides a powerful and relatively simple means to interconnect block diagrams, set model parameter values, perform model simulation, and display the outputs. A conceptual block diagram of the model is shown in Figure 5A, wherein the various components and interconnections have a direct correspondence with known retinal anatomy and physiology (Dowling 1996). It is based on the principle that the magnitude of retinal defocus can be represented by the difference in center and surround retinal excitation. The amount of surround stimulation is derived from the accommodative error obtained via the accommodative stimulus/response function (Figure 3). The difference between the center and surround excitation provides the retinal defocus signal. A *change* in this signal, and thus retinal defocus magnitude, provides the requisite sign for modulating ocular growth. The sensitivity to local retinal-image contrast is maintained at a relatively constant level by means of feedback regulation of horizontal cell gain provided by the interplexiform neurons, which relay an activity level signal from the innerplexiform to the outerplexiform layer to modulate horizontal cell sensitivity. This precludes the need for any "memory mechanism" for storing information regarding the previous levels of retinal defocus magnitude, so that its change can be discerned. The release of neuromodulator in turn results in changes in the rate of scleral proteoglycan synthesis, which causes a change in scleral growth rate. This relative growth rate is added to the ongoing and normal genetically determined ocular growth rate to provide the overall axial length growth.

A more detailed block diagram model is shown in Figure 5B. The quantitative model was tested using a repeated nearwork-induced transient myopia paradigm (55 min at near followed by 5 min at far) for overall intervals of 1, 10, 50, 100, and 500h. This progressive sequence was chosen to illustrate the minimal time needed to initiate a significant increase in axial length, as well as to demonstrate the pulse in scleral growth rate due to the repeated nearwork-induced transient myopia. The model simulations were used to demonstrate the long-term effects of these changes on scleral growth. Moreover, the effect of decreased susceptibility to nearwork-induced transient myopia (as in emmetropia or hyperopia; Ciuffreda and Wallis 1998) was investigated by reducing the gain of the 0.001-Hz filter in the innerplexiform processing stage from 10 to 0.1 and then stimulated by repeated nearwork-induced transient myopia for 500h. Various model parameters were monitored: the horizonal cell gain (representing feedback modulation from the inner to outer plexiform layer by interplexiform neurons), the rates of neuromodulator release and proteoglycan synthesis, and the relative change in axial length.

Model simulation responses to repeated nearwork-induced transient myopia for 1, 10, 50, 100, and 500 h are shown in Figures 6 through 10, respectively. Percentage change in axial length over a 0-120 h time interval is shown in Figure 11.



FIGURE 5 (A) Conceptual block diagram model of the retinal defocus pathway for regulating scleral growth. The difference between the center and surround excitation provides the retinal defocus signal. The derivative of the signal drives the release of neuromodulators,

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which provides feedback via interplexiform neurons to regulated horizontal cell gain. In addition, release of neuromodulators causes changes in the rate of proteoglycan synthesis, and in turn relative scleral growth rate. Reprinted from Hung and Ciuffreda (2000c) with permission. (B) Detailed block diagram model depicting the regulation of scleral growth rate. The retinal layers (outer to inner) are arranged from left to right, and they consist of photoreceptors, outer plexiform layer, bipolar cell layer, inner plexiform layer, and ganglion cell layer (Figure 5A) (Normann and Guillory 2002). Two pathways are needed in the model to represent the different types of signals being transmitted (Dowling 1996). The transient pathway consists of the center photoreceptor, center bipolar A, and transient ganglion (represented by a 50-Hz highpass filter); the sustained pathway consists of the center photoreceptor, center bipolar B, and sustained ganglion. Each pathway consists of a center-surround organizational structure: the horizontal cells relay surround information to center bipolar B and then on to the sustained ganglion cells; on the other hand, the amacrine cells (represented by a 50-Hz highpass filter) relay change in surround information to center bipolar A, and in turn to the transient ganglion cells. The output of center bipolar B, which represents retinal defocus amplitude, is first rectified to retain its magnitude, but not direction. This signal passes through two filters that represent the conversion from neural signal to neuromodulator release. The lowpass (representing signal transmission through the ocular tunics) and highpass (representing change-detecting neural circuitry) filters are assumed to be part of the neural circuitry in the innerplexiform layer, most likely involving amacrine cells. Neuromodulator release rate is modeled as a lowpass filter with a time constant of 1 h, and this represents the diffusion process of release from the innerplexiform layer in the retina to the choroid. The diffusion through the choroid is represented by a lowpass filter with a time constant of 10 h (L.F. Hung et al. 2000; Troilo, Nickla & Wallman 2000). The proteoglycan synthesis rate is modeled as a lowpass filter with a time constant of 20 h (Rada et al. 1992; Wildsoet 1998; McBrien et al. 1999). These time constants were estimated to provide a combined time course similar to that seen experimentally (Diether & Schaeffel 1999; Siegwart and Norton 1998; Smith and Hung 1999; L.F. Hung et al. 2000; Troilo, Nickla & Wildsoet 2000). Finally, the inverter converts a decrease in proteoglycan synthesis rate to an increase in scleral growth rate.

An important part of the model is the interplexiform feedback regulation of horizontal cell gain. The gain control and amplitude compression are regulated using a hyperbolic tangent function (not shown) for the interplexiform signal, so that for a wide range of input values, the output is compressed and limited to a range between -1 and 1. These limits are important to prevent large gain instability oscillations in the model (Stark 1968). To obtain a normalized horizontal cell gain range of 0 to 1, the output of the tanh function is multiplied by 0.5 and then added to a constant value of 0.5. The overall effect of such feedback regulation is to modulate horizontal cell gain so that, for example, a large retinal defocus signal from the interplexiform neurons would result in a decrease in horizontal cell gain. Such feedback regulation provides an automatic mechanism for obtaining relatively constant sensitivity to changes in retinal-defocus magnitude, and this is accomplished without the need for a "memory mechanism" for storing previous signal levels.

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The stimulus amplitude was defined in terms of its relative luminance over a unit of retinal area, in which a unit area represents the extent of the limit of visual acuity (about 1 min of arc linear dimension) (Westheimer 1981). For simplicity, each center and surround unit of retinal area could be assigned three luminance levels: -1, 0, or 1. The contribution from an additional unit of spatially extended surround area could be included by adding its luminance contribution to that from the immediately adjacent surround area. In this way, the surround amplitude reflected the relative amount of retinal defocus rather than retinal-image contrast per se. To simulate the rapid temporal variation in luminance over a particular retinal locus in the course of a normal viewing period, all retinal areas received a 0.1-Hz square-wave signal. A duty cycle (on-duration/total-duration) was set at 0.917 to represent 55 min of nearwork and 5 min of far viewing imposed during nearwork-induced transient myopia was applied to all stimuli. Thus, for example, the receptive field center would always consist of a ± 1 amplitude peak-to-peak (ptp) signal (i.e., a 0.1-Hz square-wave with amplitudes ranging from -1 to +1). On the other hand, the surround signal could vary depending on the amount of modulation (either 0 or 1), which represents the amount of retinal defocus. The target dioptric stimulus was converted from the amount of retinal defocus based on a typical accommodative stimulus/response curve (Figure 3). Thus, for example, at point A, the modulation was set to 0 (i.e., zero amplitude for the surround) to represent a relatively small amount of retinal defocus was set equal to 1 to represent a relatively large amount of retinal defocus.



FIGURE 5 (Continued).



FIGURES 6-10 Model simulation responses to repeated nearwork-induced transient myopia for 1, 10, 50, 100, and 500 h, respectively. For each of these figures: A shows the surround stimulus and the change in horizontal cell output; B shows the neuromodulator release and proteoglycan synthesis rates; C shows the scleral growth rate relative to the genetically determined normal growth rate; and D shows the change in axial length relative to normal. It is clear from these figures that for nearwork-induced transient myopia of 1 h (see Figures 6 and 7), although the proteoglycan synthesis and scleral growth rate have begun to change, the axial growth rate has not changed. This may reflect a time lag between the linear dimensional thickness change for scleral growth and the consequent volumetric change corresponding to axial growth rate. However, after 10 h (Figure 7D), a very small change becomes evident. The cumulative effect of nearwork-induced transient myopia on scleral growth rate is clearly seen in Figures 8D–10D. It appears that repeated nearwork-induced transient myopia over a timecourse of 20 hours can initiate a considerable change in axial length relative to normal. It should be pointed out, however, that a return to far viewing for a substantial portion of the period will reduce the growth rate toward the normal genetically based-only amount. This was found, for example, in monkeys, in which short periods (1-4h) of normal far viewing substantially reduced the effect of long periods of form-deprivation induced myopia (Smith et al. 2002). The repeated nearwork-induced transient myopia responses do not exhibit a progressive increase in axial growth rate with increased duration of nearwork-induced transient myopia stimuli. Instead, axial length plateaus after about 90 h (Figures 9 and 10). Thus, the axial growth rate will stabilize and exhibit saturation rather than becoming ever progressively greater.



FIG 7



FIG 8



FIG 9



FIG 10



FIGURE 11 Bar graph of model response shown in Figure 10D converted to percentage change of ocular axial growth versus time of repeated nearwork activity over the 120 h interval illustrating initial relative change and subsequent plateau.

DISCUSSION

There are two fundamental aspects of our incremental retinal-defocus theory that appear to contradict common conceptions regarding myopia development. First, the theory predicts that a decrease in retinal-image defocus results in increased axial growth rate and permanent myopia development. Intuitively, one would think that any decrease in retinalimage defocus, which always improves retinal-image quality, should promote normal and healthy vision development rather than produce an undesirable refractive error. The resolution to this dilemma is that the repeated cycles of decrease in retinal-image defocus over a prolonged period of time would produce myopia, whereas the transitory decreases in retinal-image defocus that occur occasionally in conjunction with prolonged periods of *maintained* small amounts of retinal defocus are consistent with the promotion of normal ocular growth. The repeated cycles of decreased retinal-image defocus are the result of repeated nearwork-induced transient myopia following sustained nearwork. This can be demonstrated by examples. First, consider a child raised in an urban environment who performs a substantial amount of nearwork. Following each cycle of nearwork-induced transient myopia, the accommodative response shifts slightly downward (Point A to B in Figure 3) on the accommodative stimulus/response function, thereby producing a slight decrease in retinal-image defocus. According to our theory, these repeated cycles of decrease in retinal-image defocus occurring over an extended period of time (days or weeks) would result in eventual axial elongation. Now consider a child raised in a rural environment, whose activities are primarily outdoors with much of the time spent under relatively sustained far-viewing conditions. In terms of the accommodative stimulus/response function, the accommodative response is only transiently shifted downward (Point A to the relatively flat region below the crossover point, i.e., beyond 1m distance; Figure 3), and is then maintained there for prolonged periods of far viewing. The resultant small amount of retinalimage defocus would remain relatively unchanged over long periods of time. Moreover, any small amounts of nearwork-induced transient myopia that may be produced would result in a shift downward on the accommodative stimulus/response function, and in this region (i.e., below the crossover point) it would actually result in an *increase* in the magnitude of retinalimage defocus. However, this increase would be hyperogenic, which would in fact oppose myopic growth. Hence, according to our theory, these farviewing effects would result in either no change or even a relative decrease in axial growth rate, as both are anti-myopigenic in nature.

Second, our theory states that neurochemical changes within the retina cascade through the vascular choroid to the sclera to result in structural changes to this outer tunic that effectively weaken its collagen network, which then leads to myopia development. Since it was found that choroidal thickness changes are in the same direction as axial length changes (Wallman 1997), it has been speculated that the choroid plays a major role in myopia development (Troilo et al. 2000; L. F. Hung et al. 2000) 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 retinalimage 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 (Wallman 1997), 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 (Wildsoet and Wallman 1995; L. F. Hung et al. 2000; Troilo, Nickla & Wallman 2000). However, this change in choroidal thickness would have *relatively little direct effect* on axial elongation.

In our theory, an important component of the effect of nearwork on permanent myopia development is nearwork-induced transient myopia. Over the past decade, a possible pharmacological basis for nearwork-induced transient myopia involving the autonomic nervous system has been proposed (Gilmartin and Bullimore 1987; Hung and Ciuffreda 1999a) (Figure 12). Parasympathetic innervation of the ciliary muscle is the primary drive to both transient and sustained accommodation. On the other hand, sympathetic



FIGURE 12 Schematic illustration of central and peripheral pathways for autonomic nervous system (ANS) innervation of accommodation. The source of autonomic innervation is the hypothalamus, which has profound connections with all central nervous system (CNS) areas. ISP represents a putative inhibitory sympathetic pathway between the hypothalamic center and the Edinger-Westphal nucleus (EWN). The first peripheral synapses occur at the ciliary and superior cervical ganglia for the parasympathetic and sympathetic pathways, respectively. Adapted from Kaufman (1992) and reproduced from Gilmartin et al. (1992), with permission.

innervation is only activated during sustained accommodation. With regard to nearwork-induced transient myopia, it inhibits and attenuates accommodative adaptation/retention following sustained nearwork, and therefore decreases the risk for transitory post task, myopic changes in the distance refractive state (i.e., far point of accommodation). Thus, a deficit in sympathetic innervation would predispose such individuals to manifest a greater degree of initial accommodative adaptation with a consequent longer time course of decay (Gilmartin and Bullimore 1987; Ong and Ciuffreda 1995, 1997). With this reduced ability to relax accommodation fully and rapidly, such an individual is more likely to incur the cumulative effects of extended periods of nearwork and manifest nearwork-induced transient myopia as was described earlier in our article (see Figure 4), and thus have more frequent and prolonged transient decreases in retinal-image defocus magnitude that are potentially myopigenic (Ong and Ciuffreda 1995, 1997; Ciuffreda and Wallis 1998; Hung and Ciuffreda 1997, 2000c).

Given the short-term and long-term differential susceptibility of refractive subgroups to nearwork-induced transient myopia (Ciuffreda and Wallis 1998; Ciuffreda and Lee 2002), and, furthermore, that it may be associated with the

development and/or progression of permanent myopia, measures should be employed to prevent or retard nearwork-induced transient myopia. These may include: (1) frequent and periodic rest breaks during prolonged nearwork (Ciuffreda et al. 1999)-for example, looking up from a CRT or book for 30-60s every 5 to 10min may prevent accommodative adaptation from occurring (Rosenfield et al. 1992), and thereby reduce the effect of nearwork-induced transient myopia; (2) for those who are already symptomatic with respect to nearwork-induced transient myopia, and whose distance vision blurs after short periods of nearwork, accommodative optometric vision therapy will provide relief (Ciuffreda and Ordonez 1998; Ciuffreda 2002); and (3) near plus lens adds, which effectively reduce the accommodative stimulus, may also help by reducing the occurrence of nearwork-induced transient myopia, and thereby the myopigenic decreases in retinal-image defocus magnitude associated with prolonged nearwork (Ciuffreda et al. 1999; Hung and Ciuffreda 2000a). Further investigations in these important clinical areas are warranted, especially in young children who are both genetically and environmentally at a high risk of developing myopia (Ong and Ciuffreda 1997; Ciuffreda and Thunyalukull 1999; Wolffsoln et al. 2003).

This review has examined in detail our incremental retinal defocus theory of myopia development. This theory is based on the concept that a decrease in retinal defocus magnitude results in a decrease in neuromodulators release in the retina, which in turn weakens the structural integrity of the sclera, thus resulting in myopia development. In contrast to previous theories based on subtle and complex processes that could not explain all of the experimental findings, our robust and relatively simple theory was able to explain all known clinical and laboratory experiments that produced environmentalinduced changes in ocular development. Moreover, our analysis showed that repeated and sustained nearwork results in residual transient myopia, which effectively decreases the retinal defocus magnitude, leading to myopia development. These sequences of neural and structural changes were simulated using a block diagram model of refractive error development, thus providing quantitative corroboration of the incremental retinal-defocus theory.

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