CONSTANT LIGHT EFFECT ON MYOPIA

Incremental Retinal-Defocus Theory Predicts Experimental Effect of Constant Light on Myopic Progression

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Abstract

The authors recently used the Incremental Retinal-Defocus Theory (IRDT) as a unifying hypothesis to predicted the effect of undercorrection of lens prescription on myopic progression (J Behav Optom 2004;15;59-63). The theory was extended to predict the effects of constant light and constant darkness on myopic progression, as recent controversy exists in the area related to infant visual development and myopia. Experimental results have shown that ocular growth under constant light as well as constant darkness produced axial elongation and corneal flattening. Yet, there has not been a satisfactory explanation for the underlying mechanisms for these results. Therefore, the IRDT was used to form the basis for a schematic model to ascertain the overall change in retinal-defocus area, and in turn axial growth rate, following repeated daily cycles under four conditions: normal, form-deprivation, constant light, and constant darkness. Furthermore, a qualitative biomechanical model of the eye was developed to investigate shape changes of the ocular tunic for these four conditions. Overall, the IRDT- based schematic analysis showed how both constant light and constant darkness could result in axial elongation and corneal flattening. And, the biomechanical model illustrated how local and global shape changes can occur under these conditions. Together, the schematic and biomechanical modeling analyses provided a clearer explanation of the underlying mechanisms for axial elongation and corneal curvature change, and in turn the development of refractive error in both animal and human studies.

Key Words

myopia, refraction, retinal-defocus, rearing conditions, vision development

INTRODUCTION

Normal eye growth requires focused retinal images of the visual scene. In the absence of such retinal imagery, the resultant form deprivation produces increased axial growth and the development of myopia.[1-7] A similar effect occurs with darkness or occlusion.[8-10] Furthermore, imposition of large plus or minus spherical lenses (e.g., > 3 D in monkeys, and > 10 D in chicks[11]) results in hyperopic or myopic growth, respectively.[6,12] Moreover, these effects occur even after the optic nerve is severed, thus precluding higher center neural feedback.[3,4]

A recent theory developed by us, called the Incremental Retinal Defocus Theory (IRDT), describes a fundamental mechanism which has been able to clarify and explain the various experimental results on axial elongation.[13-18] For example, it was able to explain the effect on myopic progression due to: imposed large plus and minus spherical lenses; imposed weak, intermediate, and strong diffusers; transient hyperopia following the imposition of a diffuser; wearing of a black occluder; removal of the crystalline lens; prolonged nearwork; and undercorrection of lens prescription.[16-18]

Briefly, the theory states that in addition to the genetically-predetermined component, the rate of axial elongation is modulated by the change in retinal-defocus area (i.e., change in the size of the retinal blur circle, corresponding to a point light source, over a time course of hours for smaller animals such as chicks, and days or even weeks for larger animals such as monkeys). The cascade of events can be described as follows: a decrease in retinal-defocus area, as can occur during an increment of genetically-preprogrammed growth over a period of time, results in a decrease in the rate of release of neuromodulators, such as dopamine, by the amacrine cells in the retina.[19] This in turn leads to a decrease in the rate of proteoglycan synthesis, a precursor of the scleral matrix material. Reduction in scleral matrix material decreases the integrity of the scleral tunic, thus resulting in an increase in axial growth rate relative to normal. The converse holds for an increase in retinal-defocus area, which will result in a decrease in axial growth rate. A summary of this process is shown in Figure 1. A detailed graphical description of the effects, over a period of time, of increase or decrease in retinal-defocus area

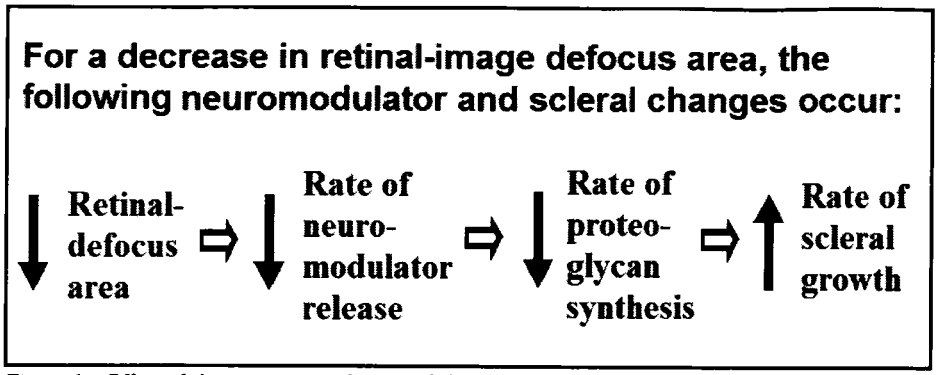

Figure 1. Effect of changes in retinal-image defocus area on scleral growth rate. Based on the Incremental Retinal-Defocus Theory. Adapted from Hung and Ciuffreda.[17]

on axial growth rate is provided in our recent article in this journal.[18] Repeated episodes of decrease in retinal-defocus area, as in the case of prolonged nearwork,[16-17] can lead to the development of myopia.

There are two known experimental results that have not yet been addressed by the IRDT. The first is the finding that under the condition of constant light, the eye exhibits enlargement, including axial elongation.[20-23] However, such axial elongation also occurs under the conditions of constant darkness and constant full occlusion. It would appear that, based on illumination levels alone, constant light and constant darkness[8-10] should have opposite effects on axial growth. Instead, they show essentially the same effect, with both producing axial elongation. Thus, illumination level per se is not a primary regulator of ocular growth rate. In addition, daytime viewing cannot be a contributing factor to the similarity in axial elongation because under the constant light condition, normal retinal defocus is present during the day, whereas under the constant darkness condition, there is an absence of retinal defocus (as well as an absence of change in retinal-defocus area). It appears instead that the common factor in these two conditions is nighttime viewing, where under both constant light with closed eyelid and constant darkness, there is a substantial reduction in contrast.

The second experimental finding that has not been addressed is the relatively severe corneal flattening that occurs under both constant light and constant darkness conditions. In a number of studies, this corneal flattening was found to result in hyperopia despite the axial elongation.[9,22,23] The exception was a study by Lauber et al.,[24] in which the eye became myopic under the constant light condition, although Li et al.[22] have attributed this to differences in the strains of chicks used in the studies.

To assess the mechanisms underlying these two experimental results systematically, both a schematic analysis and a qualitative biomechanical modeling analysis were undertaken. The findings provide an overall framework for understanding ocular growth under different rearing conditions.

METHOD AND RESULTS

Constant Light

Reconciling these results[1-7] required three observations or assumptions:

First, in all of the experiments, the animals must go through two time-interval stages: awake and sleep. During the awake stage, the visual-scene is the same under both the normal and constant light conditions. However, during the sleep stage, the normal condition provides darkness, which is analogous to dark rearing, whereas the constant light condition permits some small portion of the light to pass through the semi-transparent closed eyelid, which is similar to form deprivation under optically-degraded conditions.[1-7,25,26] Thus, the different amounts of light entering the eye during the sleep stage differentiates between these two conditions.

Second, there is a baseline level of neuromodulator activity under the darkness condition,[9,10] associated with a preprogrammed, or default, level of neuromodulator release rate. This would lead to a preprogrammed (i.e., without feedback) growth of the eyes, thereby resulting in a default rate of axial elongation. In contrast, under normal viewing conditions, there is information regarding the change in retinal-defocus which, through the emmetropization mechanism, regulates axial growth rate and maintains normal growth.

Third, it is assumed that form deprivation provides relatively unchanging, though markedly defocused, retinal images to result in a smaller change in retinal-defocus area than the default value described above, a lower neuromodulator release rate, and in turn an axial growth rate above the default rate.

The schematic diagram for a typical daily cycle (Figure 2) compares: (a) change in retinal image defocus area/neuromodulator release rate; (b) proteogly can synthesis rate, and (c) average axial growth rate under the conditions of: normal viewing, form deprivation, constant light, and darkness. Without loss of generality, the ordinates are shown in arbitrary units, and the average axial growth rate is taken as the reciprocal of the average proteoglycan synthesis rate.

In the "Normal" column in Figure 2, during the "Awake" stage, relatively large amounts of change in retinal-defocus area take place, which leads to a relatively large neuromodulator release rate. This is arbitrarily designated by a value of 2. However, during the "Sleep" stage, due to an absence of feedback regulation, the neuromodulator release rate reverts to a relatively smaller but arbitrary default value of 1. The proteoglycan synthesis rate is the result of the overall effect of diffusion and neurochemical activities, and it is represented by the average of the neuromodulator release rate over the 24 hr period, or a value of 1.50. To account for the opposite directions in which their rates change, the axial growth rate is taken as the reciprocal of the proteoglycan synthesis rate to result in a value of 0.67.

In the "Form Deprived" column during the "Awake" stage, there is constant, and therefore relatively unchanging, retinal-defocus area. This leads to a relatively low neuromodulator release rate, designated by a value of 0 (it should be noted that the choice of a value of "0" is arbitrary, but this is needed to provide average effects that are consistent with experimental results). Moreover, during the "Sleep" stage in the dark, due to an absence of feedback regulation, the neuromodulator release rate reverts to a default value of 1. The average effect of neuromodulator release rate over the 24 hr interval produces a relatively low proteoglycan synthesis

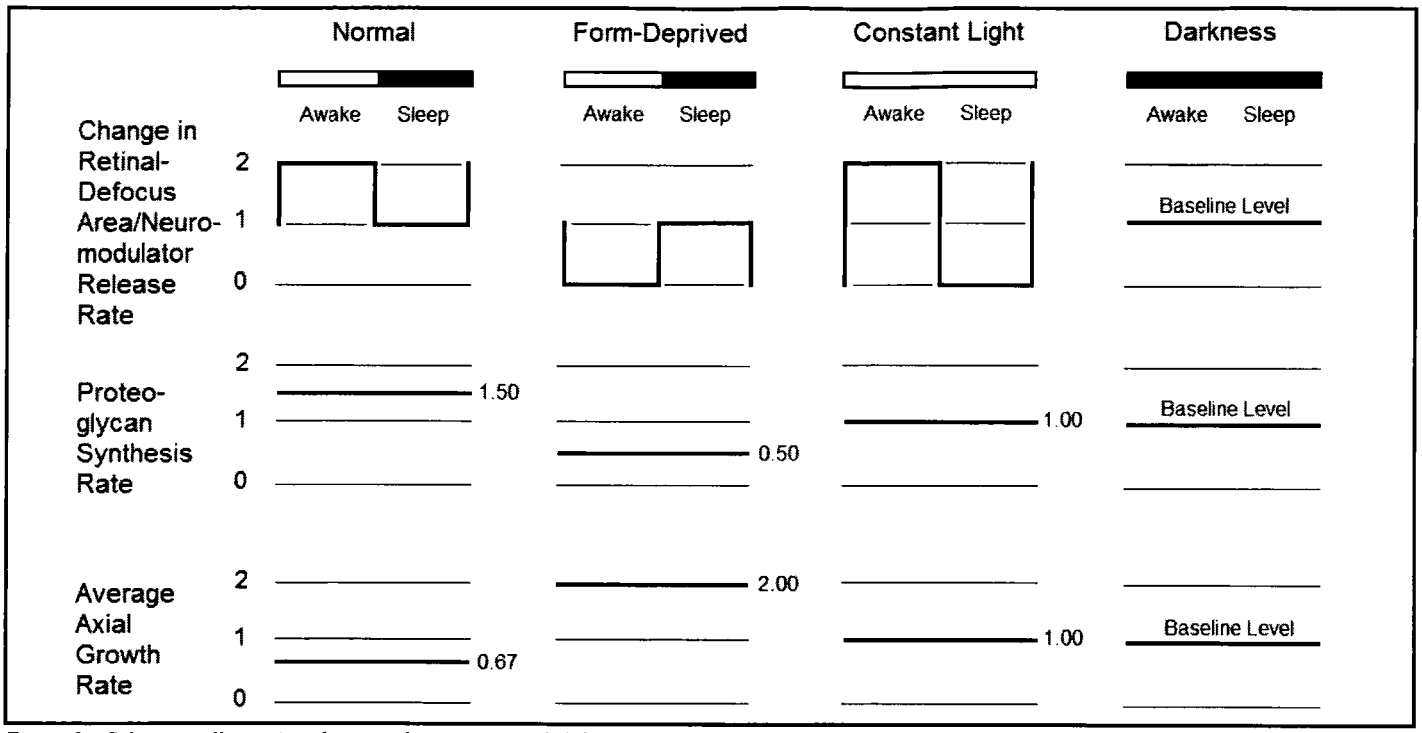

Figure 2. Schematic illustration showing change in retinal-defocus area/neuromodulator release rate, proteoglycan synthesis rate, and average axial growth rate for the conditions of normal viewing, form deprivation, constant light, and constant darkness. Arbitrary units.

rate of 0.5, which results in an axial growth rate of 2.0.

In the "Constant Light" column, the "Awake" stage is the same as that under the "Normal" condition, so that there is a relatively large amount of change in retinal-defocus area. This leads to a relatively large neuromodulator release rate, which is designated by a value of 2. Significantly, during the "Sleep" stage in the light, the light through the eyelids is assumed to result in retinal images that are similar to that for form deprivation during the "Awake" stage. Thus, the neuromodulator release rate has a value of 0. The average effect of neuromodulator release rate over the 24 hr interval results in a proteoglycan synthesis rate of 1, which results in an axial growth rate of 1.0.

In the "Darkness" column, there is essentially no difference between the "Awake" and "Sleep" stages, so the neuromodulator release rates maintains a default value of 1. This in turn leads to proteoglycan synthesis and axial growth rates of 1.

The schematic model-based analysis results (Figure 2) show that the predicted axial growth rate is slowest for normal viewing, higher for constant light and darkness, and highest for form deprivation. This is consistent with the numerous known experimental results cited earlier.

Eye Shape Following Form Deprivation and Dark Rearing

Gottlieb et al.[27] demonstrated that the change in eye shape of chicks following frontal deprivation, total form deprivation, and dark rearing were different (Figure 3, left column). Frontal deprivation (i.e., local nasal-retina defocus) resulted in eye enlargement primarily in the nasal sclera (Figure 3a); total form deprivation resulted in overall eye enlargement along with corneal steepening (Figure 3b); and dark-rearing resulted in a somewhat smaller degree of eye enlargement along with corneal flattening (Figure 3c).

A qualitative biomechanical model based on the IRDT was used to analyze and reconcile these three different shapes (Fig. 3, right column). It is based on the relative strengths of the scleral matrix in different regions of the retina as a result of the imposed optical manipulation. It is hypothesized that:

(1) Local nasal-retina deprivation results in a weaker scleral matrix in the nasal sclera relative to the other regions (Figure 3a). Hence, due to the existing normal intraocular pressure of 16 mm Hg in children,[28] the eye expands more in this local region than in other regions. This weaker region would deform more than in other regions, whereas the more rigid regions would not be so readily deformed.

(2) For total form deprivation, in which the entire retina is deprived, there is a weakening of the entire posterior region of the eye (Figure 3b). Anteriorly, the cornea is assumed to be a relatively pliable tissue which is "anchored" to the corneal-scleral junction.[29,30] Both the anterior and posterior regions of the globe are expanded by the intraocular pressure. In this situation, the approximately cylindrical mid-section in the region of the ciliary body is more than twice as rigid as the cornea and slightly more rigid than the posterior sclera.[31] Thus, the existing normal intraocular pressure acts to "extrude" the internal material in the axial direction both in the forward and backward directions (represented by the two-headed arrow). This results in both axial elongation and corneal steepening.

(3) The dark reared condition represents a default condition, whereby the growth of the outer tunic reverts to a more rounded shape, where it is assumed for simplicity that ocular rigidity and thickness are uniform for the globe[32]

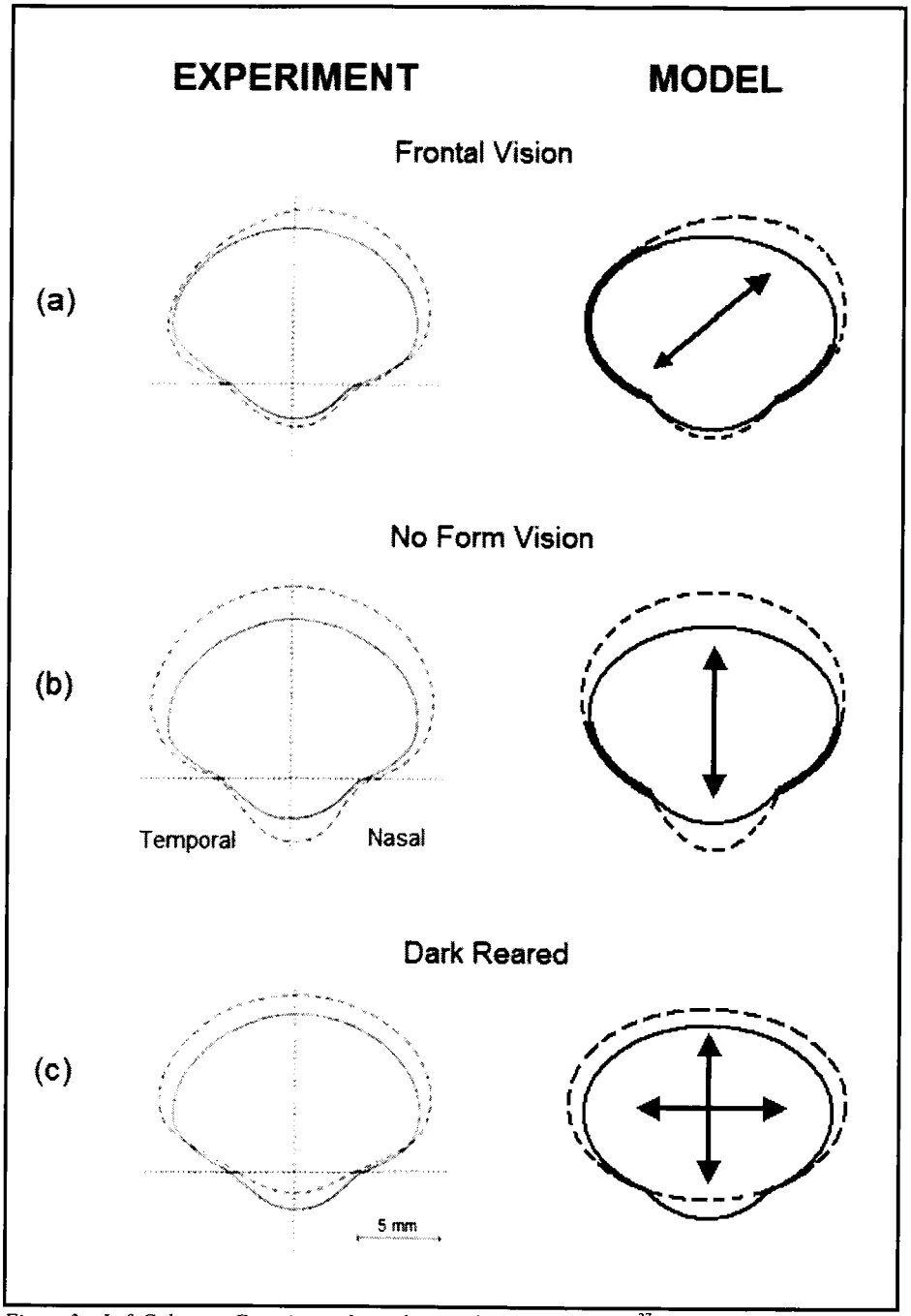

Figure 3. Left Column - Experimental eye shapes of 6-week old chicks[27] under the conditions of (a) frontal vision (nasal retina deprivation), (b) no form vision (total form deprivation), and (c) dark rearing. Solid lines indicate untreated eyes, and dashed lines represent treated eyes. Right Column - Corresponding model eye shapes. Thicker lines represent relatively stronger scleral matrix, which is less susceptible to shape changes than regions represented by thinner lines. Arrows indicate direction of expansion towards weaker regions of the ocular tunic. Note that dark reared eye (c) shows reversion to a default rounded shape.

(see dashed line; Figure 3c). Therefore, the axial elongation is accompanied by corneal flattening to provide the resultant more rounded or "squashed spheroid" shape.

These qualitative analyses of the model provide an overall view of the biomechanical factors that result in the observed ocular changes. Moreover, they are consistent with the experimental results.[27]

Corneal Flattening Under the Constant Light Condition

The constant light condition has been shown to result in ocular enlargement and corneal flattening.[20-23] These changes differ from those under both the form deprivation and constant darkness conditions. For example, during the day, the constant light condition is the same as the normal viewing condition, which contrasts with the absence of retinal defocus under the darkness condition and the large but relatively unchanging retinal defocus under the form deprivation condition. At night, diffuse illumination through the eyelid (for example in chicks and monkeys) provides broadly-distributed nearly ganzfeld-like very large retinal defocus, which is similar to that under the form deprivation condition, but different from the absence of retinal defocus under the darkness condition. Importantly, this form deprivation-like condition at night provides greater remodeling of the outer tunic of the eye due to the lower proteoglycan synthesis rate as compared to the normal eye during sleep, thus resulting in axial elongation.

While there is an ongoing axial elongation at night, the corneal shape is modified but in a different way than for form deprivation. This is because even though the constant light condition *during sleep* is somewhat similar to the *daytime* form deprivation condition, it is different in that the eyelids are *closed*. The pressure of the eyelid on the eye in human young adults has been found to be about 5 mm of Hg as compared to 0 mm of Hg (atmospheric pressure) with the eyes opened.[33] Thus, the closed eyelid forms a physical barrier in front of the eye to limit corneal growth, resulting in corneal flattening.

The significant effect of closed eyelids on corneal shape in chicks is supported by results of dark-reared experiments with open and closed eyes.[34] The closed eye was found to have a significantly flatter cornea than the fellow open eye, even while the open eye has a flatter cornea than in normal controls. Similar results were found for experimental lid closure in cats.[35] Yinon et al.[34,35] hypothesized that corneal flattening following dark rearing may be due to the degenerative process associated with the disuse of the accommodative neuromuscular apparatus. However, it is unclear how the lack of accommodation would affect corneal growth.

Thus, the expected overall effect of constant light rearing is axial elongation, as found under the form deprivation condition (see Figure 3b), but is limited in its growth at the front of the eye due to the

physical constraint of the closed eyelid. The net result is ocular enlargement at night, but with corneal flattening, which is similar to the growth pattern seen under the darkness condition (Figure 3c).

DISCUSSION

The schematic analysis and IRDT-based qualitative biomechanical model have been able to explain why both rearing in the dark and constant light result in axial elongation and corneal flattening. Axial elongation in darkness can be explained by a lack of retinal defocus information, thus resulting in a default or open-loop mode of growth. On the other hand, for the constant light condition, the greater change in retinal-defocus area during the day is offset by the lesser change at night that mimics the form deprivation condition. The average of these effects is a value equal to that of the preprogrammed level seen in the dark (see Figure 2).

Corneal flattening in darkness can be explained similarly by the lack of retinal defocus information, which results in a default mode of growth *for the entire eyeball* and a more rounded ocular shape, which corresponds to a flatter cornea. On the other hand, for the constant light condition, corneal flattening appears to be the result of the closed eyelid at night, which imposes a pressure of about 5 mm Hg,[33] and the concomitant greater remodeling of the outer tunic of the eye due to the lower proteoglycan synthesis rate as compared to the darkness, or default, condition. The eyelid may provide sufficient inward pressure to counteract *in part* the outward intraocular pressure of about 16 mm Hg in children.[28] Thus, while the diffuse illumination effectively causes ocular enlargement similar to that for form deprivation, it is restricted somewhat in its forward growth by the closed eyelid, resulting in corneal flattening. Moreover, the eyelids of children may be more flexible and have increased compliance, thus resulting in a lower lid pressure to oppose the forward ocular growth, which may in part be responsible for the faster rate of myopic growth in children than in young adults.[36]

There has been speculation that the effect of constant light in animals will also be manifest in infants reared with a nightlight.[37] Indeed, the results of a parental questionnaire revealed a relationship between nightlight use and myopia development. Presumably, this is due to axial elongation with a relatively small amount of corneal flattening as described earlier. On the other hand, others have found no relationship between the nightlight use and refractive development.[38,39] The difference between these two contradictory results may be due in part to differences in location, angle of illumination, and illumination levels of the nightlights used in the studies. It should be noted that the experimental illumination levels found during the sleep stage in the animal experiments are much higher than those found for nightlight use in human infants. For example, in the Li et al.[22] study in chicks, the illumination level was given as 700 lux. On the other hand, the child nightlight illumination level is estimated to be about 10 lux (http://www.pc.ibm.com/ww/healthycomputing/). These differences in illumination conditions may account for the differences seen in the increase in axial growth rate in chicks raised under the condition of constant light[20-23] and the conflicting results found in children raised with conventional nightlight.[38,39] Moreover, the study that suggested a relationship between nightlight use and myopia development[37] also showed a higher percentage (15%) than the other studies[38] (3.7%) of infants who were raised under full room illumination at night.

Overall, the schematic analysis and the IRDT-based qualitative biomechanical model have provided a rational explanation for the differences in eye growth under the conditions of: normal viewing, form deprivation, constant light, and dark rearing. These approaches provide a coherent framework for the understanding of the myriad of different experimental results of the effects of optical and physical manipulations on ocular growth in animals and humans.

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