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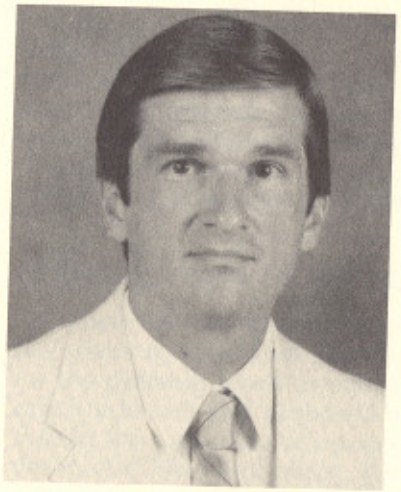
RETINAL IMAGE-MEDIATED OCULAR GROWTH AS A POSSIBLE ETIOLOGICAL FACTOR IN JUVENILE-ONSET MYOPIA



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ABSTRACT. Degradation of retinal imagery has been shown to induce myopia in animals by axial elongation through ocular growth. The correlation of the mechanisms of this animal model of myopia and of juvenile onset myopia in humans is not obvious. This paper outlines a hypothesis that bridges this gap and presents a variety of clinical observations consistent with this hypothesis of ocular growth as the mechanism of childhood myopia progression.

RETINAL IMAGE-MEDIATED OCULAR GROWTH AS A POSSIBLE ETIOLOGICAL FACTOR IN JUVENILE-ONSET MYOPIA

INTRODUCTION

Despite the high prevalence of myopia (25 to 30% among young adults in the United States)[1-5] and the considerable attention it has received from vision scientists and clinicians, the determination of its etiologies remains elusive. For instance, the chapter on etiology in Curtin's book on myopia[6] contains 813 citations, but offers no definitive statement on the etiology of juvenile onset myopia. Likewise, treatment regimens designed to slow the progression of myopia have shown negative or inconsistent results.[7-11]

CLASSIFICATION OF MYOPIA

There are undoubtedly several types of myopia with varying etiologies. Necessary to their understanding is an appropriate classification system for the different types of myopia. Grosvenor[12] reviewed existing classification schemes and proposed a new one based on age of onset. In this system the categories of myopia are congenital, youth-onset, early adult-onset, and late adult-onset. Youth-onset or juvenile-onset myopia is the most common form of myopia,[5,12,13] with onset anywhere from about six years of age to the teenage years. Once myopia appears, it increases, or progresses, in amount until its progression stops or slows in the middle or late teens.[14-19] It usually develops to about one to four diopters, and is found with normal corrected visual acuity and normal ocular health. Examples of patterns of childhood myopia progression are shown in Figure 1.

MYOPIA INDUCED IN ANIMALS BY ALTERATION OF OCULAR IMAGERY

One potential technique for investigation of myopia etiology is the development of appropriate animal models. Myopia has been induced in a variety of animal species.[6,20-22]

The common denominator in recent experimental manipulations to induce myopia in animals has been the degradation of retinal imagery.

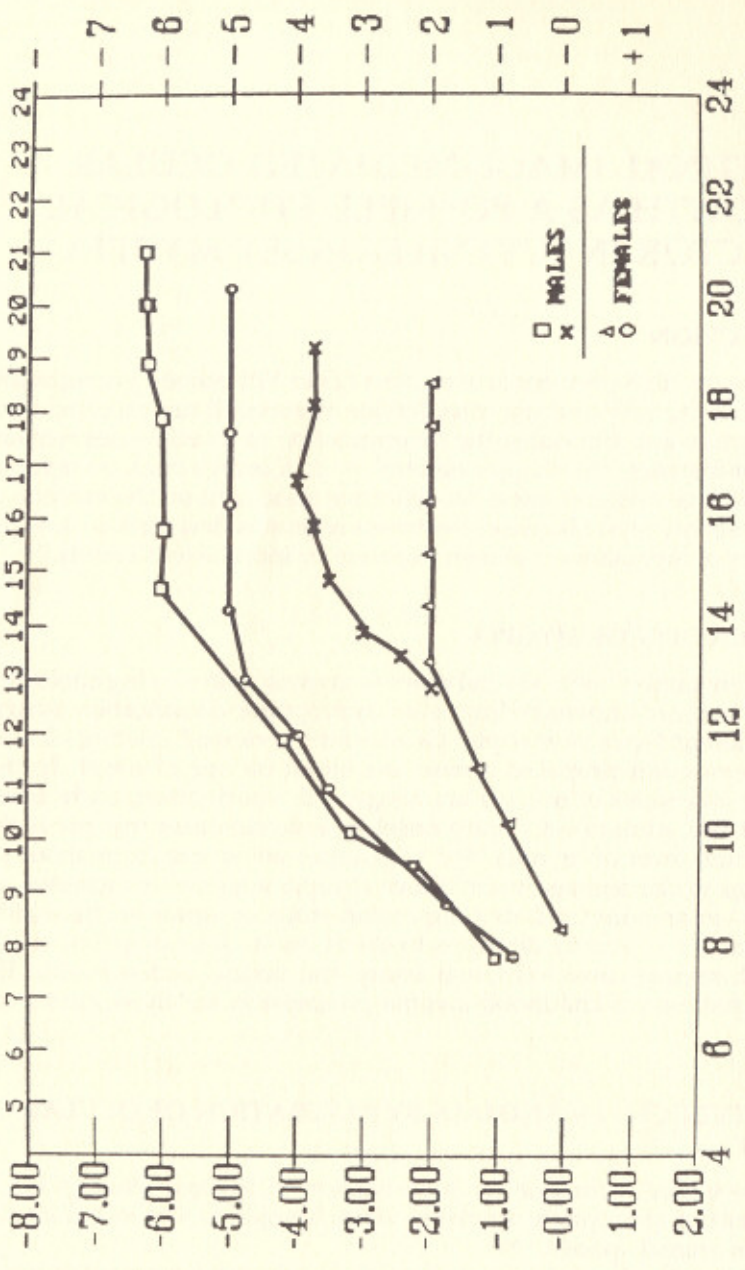

FIGURE 1. Examples of refractive change as a function of age in childhood myopia progression. Refractive error in diopters is on the y-axis, and age in years is on the x-axis. Each set of common symbols represents refractive findings for one patient.

This has been achieved, for instance, by eyelid suture, partial corneal opacification, and attachment of translucent occluders. Myopia has been produced in chickens,[23-28] cats,[29,30] tree shrews,[31] and monkeys.[32-37] In monkeys this line of investigation began with the observation that eyes under sutured eyelids develop axial myopia.[32] Thermal or pressure effects were ruled out when it was found that lid suture did not lead to myopia when the animals were dark-reared,[33] and that corneal opacification induced axial elongation of the eye, and presumably myopia.[34] Smith et al.[35] noted that for monkeys the earlier form deprivation is initiated and the longer it is maintained, the greater is the amount of the myopia that develops.

Animal experimentation suggests that retinal image alteration leads to axial elongation by ocular growth through local mechanisms. Wallman et al.[24] found that when white translucent occluders were applied to selectively deprive the nasal retina or temporal retina of developing chicks, only the deprived part of the eye showed myopia. Vitreous depth increased only on the side of the eye deprived of normal visual input. Optic nerve section does not prevent development of myopia in chicks deprived of form vision.[27]

Local mechanisms are also suggested by the work on rhesus monkeys by Raviola and Wiesel.[37] Various denervation procedures, including ciliary ganglion removal, superior cervical ganglion removal, section of the roots of the trigeminal nerve, optic nerve section, and removal of the striate cortex, did not prevent the development of axial myopia from lid suture. The work of Stone et al.[38] in monkeys may point to a possible mechanism. They found increased levels of vasoactive intestinal polypeptide in retinal amacrine cells in eyes deprived by eyelid suture. Some growth inducing substances, or growth factors, are polypeptides.[39]

The animal experiments described above have produced blur or form deprivation by various forms of translucent occlusion. Schaeffel et al.[40] demonstrated that optical defocus will also lead to myopia in chicks. By application of -4 and -8D lenses they induced a small amount of myopia. The refractive result was approximately the same regardless of whether the lenses were applied monocularly or binocularly. Animals exposed to lenses of +2 and +4 diopters developed a small amount of hyperopia. The posterior nodal distance was greater in eyes treated with minus lenses than in eyes treated with plus lenses. This suggests that axial elongation during development is responsive to the direction of optical defocus. Schaeffel et al. [40] discussed the possibility of accommodation serving as the source of this directional sensitivity.

Human correlates of the high myopia produced in animals by form deprivation exist in humans with eyelid and ocular media anomalies. The severe retinal image degradation caused by lid hemangiomas,[41] ptosis,[42] neonatal lid closure,[43] retinopathy of prematurity,[44,45] and other ocular anomalies[46,47] is associated with a high myopia (generally five diopters or more) in humans. Like the animal model, this form deprivation myopia is due to axial elongation of the eye. (In retinopathy of prematurity there is

both a reduction in anterior corneal radius associated with arrested ocular development and an axial elongation associated with media and retinal changes.) There does not seem to be an obvious correlation of the animal model of myopia with the much more common occurrence of youth onset myopia developing in an otherwise healthy eye. The hypothesis outlined in the next section appears to bridge a gap between form deprivation myopia in animals and clinical observations on juvenile-onset myopia patients.

A NEW HYPOTHESIS FOR THE ETIOLOGY OF JUVENILE-ONSET MYOPIA

Myopia undoubtedly has both genetic and environmental determinants.[48-50] An environmental factor often hypothesized to play a role is near work.[1,3,6,48,49,51-58] Myopic persons often have occupations requiring near work, myopes tend to spend more time reading and in other nearpoint activities, and myopes tend toward better reading ability and scholastic achievement than non-myopes. Myopia is more common in populations that do greater amounts of near work. Though cause and effect have never been definitively demonstrated, a role for near work in myopia development would appear to be a reasonable working assumption.

For clear vision during nearpoint viewing, the dioptric accommodative response must approximate the dioptric stimulus to accommodation. A small lag of accommodation, the dioptric amount by which accommodative response is less than the accommodative stimulus, is normal and will allow clear retinal imagery due to the depth of focus of the eye. Under typical conditions of pupil size, illumination, contrast, and acuity demand, the accommodative response for an accommodative stimulus of 2.50 diopters is approximately 2.25 diopters.[59,60] If the lag of accommodation significantly exceeds this, the quality of retinal imagery may be compromised. Accommodative dysfunction might then lead to myopia by a mechanism similar to that in form deprivation myopia in animals.[50] A lack of contrast in the defocused retinal image might lead to the increased production of growth-inducing substances, or growth factors, which in turn would cause ocular axial elongation.[50,61] In humans, this would most likely be a function of the central retina because foveal vision is used for reading, and objects in the peripheral field are ordinarily not clearly imaged on the retina.[62,63] The slight retinal image degradation associated with accommodative disorders might be expected to produce a lower amount of myopia than that in media opacities; this, of course, is the case in ordinary juvenile- onset myopia. The study by Schaeffel et al.[40] would suggest directional sensitivity of axial growth. That is, if ocular images are in focus at a point behind the retina, growth of the posterior segment would be induced to move the retina in the direction of the focused image. If this is true in humans the optical defocus caused by under-correction of myopia for distance would not result in axial elongation. The direction of optical defocus resulting from insufficient accommodation for nearpoint would require axial elongation to achieve focus on the retina.

Age (Yrs)	Hirsch, 1952 (n = 9,552)		Young et al., 1954 (n = 652)		Langer, 1966 (n = 263)	
	Girls	Boys	Girls	Boys	Girls	Boys
5-6	6.15	7.43	4.17	0.00	2.04	0.00
7-8	9.71	11.02	2.60	5.62	3.97	3.08
9-10	17.18	15.68	19.44	9.68	12.20	11.68
11-12	21.60	20.74	20.00	27.27	29.18	20.48
13-14	25.36	22.53	25.71	28.57	34.42	34.30

TABLE 1. Prevalence of myopia in percent as a function of age in school children in the Los Angeles area (Hirsch[64]), in Pullman, Washington (Young et al.[65]), and in Leaside, Ontario, Canada (Langer[66]). The Hirsch and Langer data are the percentages of children with myopia of any amount. Myopia was defined in the Young et al. study as myopia of over one diopter.

CLINICAL OBSERVATIONS CONSISTENT WITH THIS HYPOTHESIS

Definitive proof of this hypothesis will be very difficult to obtain. A feasible first step is to examine whether observations on myopia patients are consistent with this hypothesis.

Ages of Onset and Cessation of Childhood Myopia Progression

If the growth factors associated with axial elongation of the eye are synergistic with human growth hormone or somatomedin, then an increase in incidence of myopia would be expected at the times of maximum body growth, and the childhood progression of myopia would be expected to stop or slow when the adolescent growth spurt stops.

Incidence may be inferred from age-related prevalence data. Such data, from three different cross-sectional studies,[64-66] are summarized in Table 1. (Langer's thesis[66] also contained some longitudinal data.) Incidence may be presumed to be greatest at the ages at which prevalence shows the greatest increases. Perusal of Table 1 suggests that the greatest incidence of myopia in girls precedes that in boys in all three populations. The adolescent growth spurt begins about two years earlier in girls than in boys.[67,68]

Once myopia appears, it increases in amount (childhood myopia progression) until the middle or late teens. This can be visualized in Figure 1.

We[15] calculated an index of the age at which childhood myopia progression ceases or slows appreciably. We called this the cessation age, which was calculated using four different graphical and statistical techniques from longitudinal data for several individuals from private practice patient data. One of these methods defined cessation age as the point at which a linear regression of refractive error on age for points below 15 years of age intersected a line of zero slope through the mean amount of myopia at observations after 17 years of age. This was determined individually for patients with three or more refractions before 15 years of age. The mean cessation age was 16.7 years (n = 66, SD = 2.1) for males and 15.2 years (n = 57, SD = 1.7) for females. These are similar to the ages at which the adolescent growth spurt ends.[67,68]

Age of Cessation of Ocular Growth

The progression of myopia in children is due to greater than normal axial elongation of the eye or axial elongation which is inadequately compensated for by reduction in the refractive power of the eye.[19,69] On the basis of the stated hypothesis, it would be expected that ocular growth in myopes would cease at about the same time as the cessation of general body growth and the cessation of childhood myopia progression.

A first glance at the literature would suggest that ocular growth stops before this. Based on cross-sectional and some longitudinal data, Sorsby and his colleagues[70,71] suggested that increases in ocular axial length stop by 13 years of age or before. This inference was based on limited data past 14 years of age, and on a limited number of myopes. Larsen,[72] reporting on his cross-sectional study of axial length, proposed that ocular growth ceases at about 13 years. However, no data after 13 to 14 years of age were reported, and the majority of subjects appeared to be emmetropes and hyperopes.

Thus, childhood myopia progression generally ceases at 15 to 17 years, while literature based largely on non-myopes suggests that ocular growth stops by 13 years of age. A longitudinal study of 18 myopic eyes by Tokoro and Suzuki[73] would seem to indicate that cessation of childhood myopia progression coincides with the cessation of ocular axial elongation. While this question was not specifically addressed in the paper, Tokoro and Suzuki[73] published composite plots of refractive error vs. age and of axial length vs. age. Visual inspection suggests that plateaus occur in both graphs at about the same ages (about 15 to 17 years). To attempt to reconcile this difference, we[74] have collected cross-sectional data on axial length as a function of age from available literature sources and from patients seen in our clinic. We now have a total of 1309 observations. As a preliminary analysis, we calculated the mean axial length as function of age, first for all refractions from all sources, and secondly for myopes from all sources. We calculated linear regression equations of axial length on age using various combinations of consecutive ages with at least ten observations

before the age of 16 years. We determined the regression equation that had the highest coefficient of correlation. The means and regression lines for males with myopia are illustrated in Figure 2. We found cessation ages by determining the points at which the regression equations intersected the mean axial length for observations at and after 17 years of age. The cessation ages thus determined are summarized in Table 2. The cessation ages for increases in stature are also given in Table 2. Mean refractive error, axial length, and height as a function of age are given for male myopes in Figure 2.

When patients of all refractions are considered the derived cessation ages of axial elongation are similar to the ages at which Sorsby and his colleagues and Larsen suggested the eye stops growth. The cessation ages of ocular growth for myopes are later and are close to the mean cessation ages for childhood myopia progression found by Goss and Winkler,[15] with an earlier cessation in females. The cessation ages for ocular growth in myopes are similar to the cessation ages for increase in height.

Effect of Bifocal Lenses on Childhood Myopia Progression

One of the treatment regimens for attempted myopia control is the prescription of bifocal lenses. Reports on the efficacy of this method have shown considerable disagreement.[7,9-11,75,76] One can only say that it is not consistently successful. Potential explanations for the differing results from study to study include investigator bias, the manner in which the bifocals were used, and the types of patients studied.

Work by Roberts and Banford[77] and by Goss[78] suggest that some level of myopia control may be achieved in esophoric patients and patients with accommodative insufficiency. Using data from their patient files, Roberts and Banford calculated rates of progression in diopters per year with age factored out by a formula for the relation of refractive change and age from correlation analysis. The mean rate for single vision lens wearers was -0.405 D/yr, while for bifocal wearers it was -0.314 D/yr. The rates for patients separated by nearpoint phoria are given in Table 3. Rates were less minus for esophores wearing bifocals. They also reported that bifocals reduced the rates for patients with accommodative insufficiency as diagnosed with nearpoint binocular cross cylinder test.

Goss[78] reported on linear regression derived rates of myopia progression (diopters per year) for patient data from three private optometry practices. The mean rate for all single vision lens wearers did not differ significantly from the mean rate for all bifocal lens wearers. For nearpoint esophores the mean rate with bifocals was less than that with single vision lenses (Table 3). Data were also separated by binocular nearpoint cross cylinder net, which was defined as the difference between the gross cross cylinder finding and the binocular maximum plus subjective refraction to best visual acuity. The mean rate with bifocals was less than that with

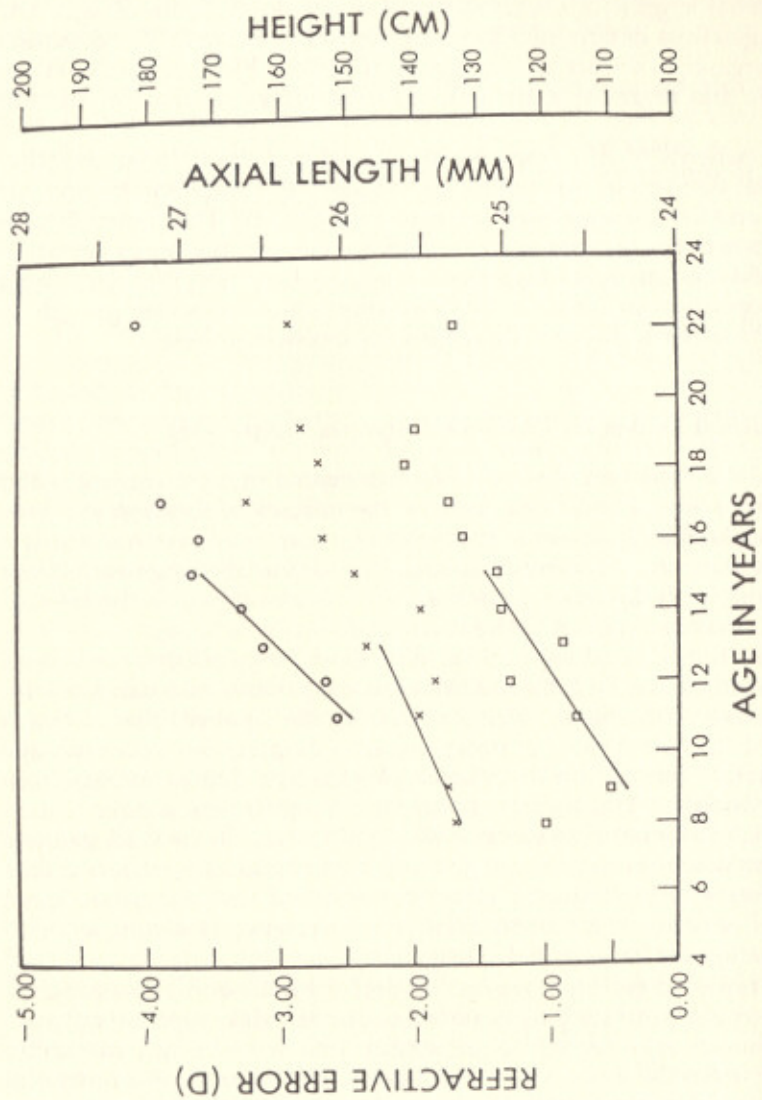

FIGURE 2. Mean axial length in mm (squares), mean refractive error in diopters (X symbols), and mean height in cm (circles) as a function of age in male myopes. Points were plotted for each mean which was determined from at least ten observations. The plotted regression lines are the regressions with the highest coefficient of correlation of each dependent variable with age using various combinations of consecutive age levels up to 16 years. The points plotted at 22 years of age are the means for all observations at 20 years of age and older.

	Males	*Females*
Cessation age of axial elongation in myopes	16.9	14.0
Cessation age of axial elongation in myopes and non-myopes combined	12.7	11.4
Cessation age of increases in height in myopes	16.2	13.8
Cessation age of increases in height in myopes and non-myopes combined	15.7	14.0

TABLE 2. Cessation ages (in years) of ocular growth as assessed by axial length measurements and of general body growth as assessed by height measurements.

single vision lenses for patients with cross cylinder nets of over +0.50 D (see Table 3).

Morgan[79] gave a normal range for the nearpoint binocular cross cylinder of +0.25 to +0.75 diopters over the subjective refraction for distance. Patients with higher plus cross cylinder nets most likely have higher lags of accommodation.[80,81] These are the cases in which the mean rates are lower in magnitude in bifocal wearers. A plus add in bifocal form would improve the quality of retinal imagery in patients with an anomalously high lag of accommodation by reducing the amount of optical defocus. This might then stop the mechanism hypothesized above.

Accommodative disorders prior to onset

Central to the stated hypothesis is that accommodative dysfunction would precede myopia onset. Clinicians have reported observing accommodative disorders in juvenile patients before they became myopic.[82-85] A number of studies[86-91] have reported differences in accommodation and vergence function examined in the laboratory in different types of refractive errors in adults, but this has not been examined quantitatively in children before juvenile onset of myopia. We have begun a study comparing clinical accommodation and convergence findings in children who become myopic and children who remain emmetropic. If this study yields a positive result,

	Single vision lens wearers			Bifocal wearers			Stat. sig. of difference
	n	Mean	SD	n	Mean	SD	in means
Roberts and Banford[77]							
All patients	396	-0.41	----	85	-0.31	----	----
Exo and ortho	181	-0.41	----	17	-0.38	----	----
Esophoria	167	-0.48	----	65	-0.28	----	----
Goss[78]							
All patients	52	-0.44	0.26	60	-0.37	0.24	n.s.
≥ 6 exophoria	9	-0.47	0.31	3	-0.48	0.22	n.s.
0-6 exophoria	27	-0.43	0.21	18	-0.45	0.27	n.s.
esophoria	10	-0.54	0.30	35	-0.32	0.20	$p<0.05$
cr. cyl. net<0.50	23	-0.31	0.25	6	-0.41	0.22	n.s.
cr. cyl. net≥0.50	16	-0.48	0.30	36	-0.25	0.17	$p<0.01$

TABLE 3. Mean rates of childhood myopia progression in diopters per year as a function of nearpoint phoria and nearpoint binocular cross cylinder net (numerical difference between the nearpoint binocular cross cylinder result and the distance binocular subjective refreaction). Standard deviations and statistical significance levels were not given in the original Roberts and Banford publication. Phoria and cross cylinder data were not available for some patients.

additional questions to be asked would be how much defocus is necessary to activate this mechanism and whether appropriate treatment regimens could prevent juvenile-onset myopia.

CONSISTENCY OF THIS HYPOTHESIS WITH A FEEDBACK HYPOTHESIS FOR EMMETROPIZATION

Various hypotheses have been put forward to explain the leptokurtic distribution of refractive errors, with predominance of emmetropia.[92,93] A number of studies have reported inverse correlations of axial length with corneal power and with lens power.[93-97] However, computer simulation by Berck[98] failed to find leptokurtosis of refractive errors as great as observed levels in the population when refractive errors were calculated with correlation of components as observed by Sorsby et al.[95] That is, correlations of components are not sufficient to account completely for emmetropization. Stenstrom[99] and Araki[96] reported leptokurtic distributions of axial length. Sorsby[95] suggested that axial length was normally distributed, but a recent re-analysis of Sorsby's data by Carroll[100] yielded a leptokurtic distribution. Leptokurtosis of ocular axial length may imply that some feedback mechanism guides ocular growth. A number of authors [35,37,46,47,101,102] have proposed that the quality of retinal imagery provides such feedback.

SUMMARY AND COMMENTS

Myopia has been induced in laboratory animals by form deprivation. This animal model so far has not been successfully related to the common juvenile-onset myopia in humans. This paper has presented a hypothesis that juvenile onset myopia is related to slightly blurred (defocused) retinal imagery secondary to accommodative dysfunction, through a mechanism of retinal image-mediated ocular growth. While definitive support for this hypothesis is lacking, clinical observations consistent with this hypothesis have been presented. These observations do not rule out other hypotheses, but the hypothesis given here appears to deserve further investigation.

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