ESSENTIALS IN OPHTHALMOLOGY

G. K. KRIEGLSTEIN · R. N. WEINREB
Series Editors

Glaucoma | Cataract and Refractive Surgery | Uveitis and Immunological Disorders | Vitreo-retinal Surgery | Medical Retina | Oculoplastics and Orbit | **Pediatric Ophthalmology, Neuro-Ophthalmology, Genetics** | Cornea and External Eye Disease

Pediatric Ophthalmology, Neuro-Ophthalmology, Genetics

Edited by
B. LORENZ
A.T. MOORE

Springer

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B. Lorenz · A.T. Moore (Eds.)

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With 89 Figures, Mostly in Color,
and 25 Tables

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Foreword

Essentials in Ophthalmology is a new review series covering all of ophthalmology categorized in eight subspecialties. It will be published quarterly; thus each subspecialty will be reviewed biannually.

Given the multiplicity of medical publications already available, why is a new series needed? Consider that the half-life of medical knowledge is estimated to be around 5 years. Moreover, it can be as long as 8 years between the description of a medical innovation in a peer-reviewed scientific journal and publication in a medical textbook. A series that narrows this time span between journal and textbook would provide a more rapid and efficient transfer of medical knowledge into clinical practice, and enhance care of our patients.

For the series, each subspecialty volume comprises 10–20 chapters selected by two distinguished editors and written by internationally renowned specialists. The selection of these contributions is based more on recent and noteworthy advances in the subspecialty than on systematic completeness. Each article is structured in a standardized format and length, with citations for additional reading and an appropriate number of illustrations to enhance important points. Since every subspecialty volume is issued in a recurring sequence during the 2-year cycle, the reader has the opportunity to focus on the progress in a particular subspecialty or to be updated on the whole field. The clinical relevance of all material presented will be well established, so application to clinical practice can be made with confidence.

This new series will earn space on the bookshelves of those ophthalmologists who seek to maintain the timeliness and relevance of their clinical practice.

G. K. Krieglstein
R. N. Weinreb
Series Editors

Preface

In an era of increasing subspecialization pediatric ophthalmology stands out as the one area of ophthalmology where the generalist holds sway. The pediatric ophthalmologist must have a good working knowledge of general ophthalmology, have an understanding of visual development, visual electrophysiology and molecular genetics and be comfortable with dealing with children with a wide range of systemic disorders. It is a major challenge to keep up to date in all these areas. The aim of this monograph is to highlight recent advances in key fields of pediatric ophthalmology and inherited eye disease and to present this material in a concise readable format. The chapters encompass both pediatric ophthalmology and inherited eye disease; neuro-ophthalmology will be covered in detail in the next volume we edit.

Retinopathy of prematurity (ROP) has become more prevalent as advances in neonatal care have led to the survival of increasing numbers of very-low-birthweight preterm infants. This monograph includes reviews of current knowledge of the pathogenesis of ROP and screening and treatment protocols. There are also updates on the management of pediatric ocular tumors, infantile cataract and glaucoma, conditions which are best managed in specialized tertiary referral centers. One of the commonest eye problems in childhood is refractive error and amblyopia. This volume includes a review of current knowledge of the causes of myopia in experimental animal models and the implications for the understanding of the pathogenesis of myopia in man. There are also chapters on preschool vision screening and management of amblyopia.

Advances in molecular biology have led to improved understanding of the pathogenesis of inherited eye disease, and we have included chapters summarizing recent advances in understandings of the molecular genetic basis of early onset-retinal dystrophies and childhood retinal detachment. There is also a chapter highlighting the role of ocular electrophysiology in the investigation of visual loss in infancy. Finally, we cover two areas of pediatric ophthalmology where ophthalmologists work closely with their pediatric colleagues, firstly congenital infections affecting the eye and secondly the role of the ophthalmologist in assessing children with suspected non-accidental injury.

The individual chapters are written by leading authorities in their field. We are grateful to them for their excellent contributions and also to the publishers for their encouragement and support.

Birgit Lorenz
Anthony T. Moore

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Development of Ocular Refraction: Lessons from Animal Experiments

1

Frank Schaeffel, Howard C. Howland

Core Messages

- There is overwhelming evidence in both animal models and humans that refractive development and axial eye growth are under visual control
- The retina can analyze the sign and amount of defocus over time and control the growth of the underlying sclera
- Myopia is generally increasing in the industrialized world, in particular in the Far East
- Although genetic factors modulate the predisposition to become myopic, the high incidence of myopia in the industrialized world is likely to be due to environmental factors
- There are two major strategies to interfere with myopia development: (1) reducing "critical visual experience" (which is about to be defined). More individually adapted spectacle corrections may be a way since they can reduce progression of myopia by up to 50% in selected children. (2) inhibiting axial eye growth pharmacologically. Atropine is effective, but the mechanism of its action is not understood and its side effects preclude prolonged application

1.1 Introduction

The size of the organs in the body is continuously regulated to match their functional capacity as required (review: Wallman and Winawer [79]). There is, however, probably no other organ so precisely controlled in size as the eye: to achieve full visual acuity, its length must be matched to the optical focal length of cornea and lens with a tolerance of about a tenth of a millimeter (equivalent to 0.25 D). A normal-sighted (emmetropic) eye that increases in length by more than this amount will be slightly myopic and experience a detectable loss of visual acuity at far distances.

Until about 1975, it was thought that this match was achieved by tight genetic control of growth, even though this appeared an improbable (or improbably impressive) achievement. About this time, it was discovered that, in monkeys whose lids were monocularly fused to study the development of binocular neurons in the visual cortex, the deprived eyes became longer and myopic [84]. This observation stimulated research into myopia in animal models. The idea was that eye growth, and therefore also refractive development, might be under visual control which is accessible to experimental studies in which the visual experience is intentionally altered. It also revived an older discussion as to whether myopia is environmental or genetic.

Today, despite the results from animal models that demonstrate visually controlled eye growth, this discussion has not come to an end (e.g., [42]). Major studies in the United States concluded that "heritability was the most important factor" in myopia development and that only less than 20% can be modulated by visual experience (Orinda study [43]; twin studies, e.g., [18]). In contrast, a recent major review of the literature reaches the conclusion that the significant increase in the incidence of myopia in the last 40 years must be due to environmental factors [39].

By using animal models, a lot has been learned about the mechanisms of visual control of eye growth. However, the definition of the visual cues that make the eye grow longer in children is more difficult than expected. Nevertheless, the observations in animal models were often unexpected and gave rise to new theories and ideas about human myopia development. At least, a number of suggestions can be derived from the experimental results in animals. They will be described in this chapter but, first, the basic features of the mechanisms of visual control of eye growth in animal models will be summarized.

1.2 Overview on the Experimental Results in Animal Models

1.2.1 What Is the Evidence for Visual Control of Refractive Development and Axial Eye Growth?

It was first demonstrated in young chickens that fitting the animals with spectacle lenses that impose a defined amount of defocus on the retina made the eyes grow so that the imposed defocus was compensated [23, 56].

In the case of a negative lens, the plane of focus of the projected image is shifted, on average, behind the retina. It was found that axial length grew faster than normal, apparently to "catch the new focal plane." Cornea and lens did not show biometric or optical changes. The longer eye was then myopic without the negative lens in place but was about in focus with the lens. The compensation of a negative lens of 4 D took 3–4 days. In the case of a positive lens, axial eye growth was inhibited until the focal length of cornea and lens had sufficiently increased to produce hyperopia of the magnitude that was necessary to compensate for the lens power.

Developmental adaptation of refractive state by visual cues was first assumed to be a special feature of the bird eye. It was subsequently shown that young monkey eyes could also compensate for imposed defocus (Fig. 1.1) [21, 66]. Given that chicks and monkeys are phylogenetically not closely related, and that monkeys are much closer to humans than to chicks, it seems very likely that also the growing human eye can compensate for imposed defocus.

1.2.2 Which Kind of Visual Stimulation Induces Refractive Errors in Animal Models?

There are two different visual stimulations that interfere with axial eye growth: either globally degrading the retinal image sharpness and contrast, or imposing defined amounts of defocus.

1.2.2.1 Stimulation of Axial Eye Growth by Retinal Image Degradation

Lid fusion, as performed in the initial experiments [84], is an experimental manipulation with several effects: the retina no longer has access to spatial information (although it is not completely light-deprived), the mechanical pressure on the cornea is changed, and the metabolic conditions and temperature in the eye may be different. Although each of these factors could interfere with eye growth, it was found that the most important component was the deprivation of the retina of sharp vision and contrast. Accordingly, this type of myopia has been called form deprivation myopia (FDM) because form vision is no longer possible. In the meantime, it became clear that even a minor reduction of image sharpness and contrast may already stimulate axial eye growth: "deprivation myopia is a graded phenomenon" [67] and this has been shown in both chickens [3], and rhesus monkeys [67]. Therefore, the term "form deprivation myopia" may be an exaggerated description of the visual condition and could be replaced by "deprivation myopia" since this term makes no assumptions about the exact nature of the deprivation.

Deprivation myopia has been observed in almost all vertebrates that have been studied [79]. It is commonly induced by placing a frosted occluder in front of an eye for a period of several days or weeks. The speed by which deprivation myopia develops depends on the species

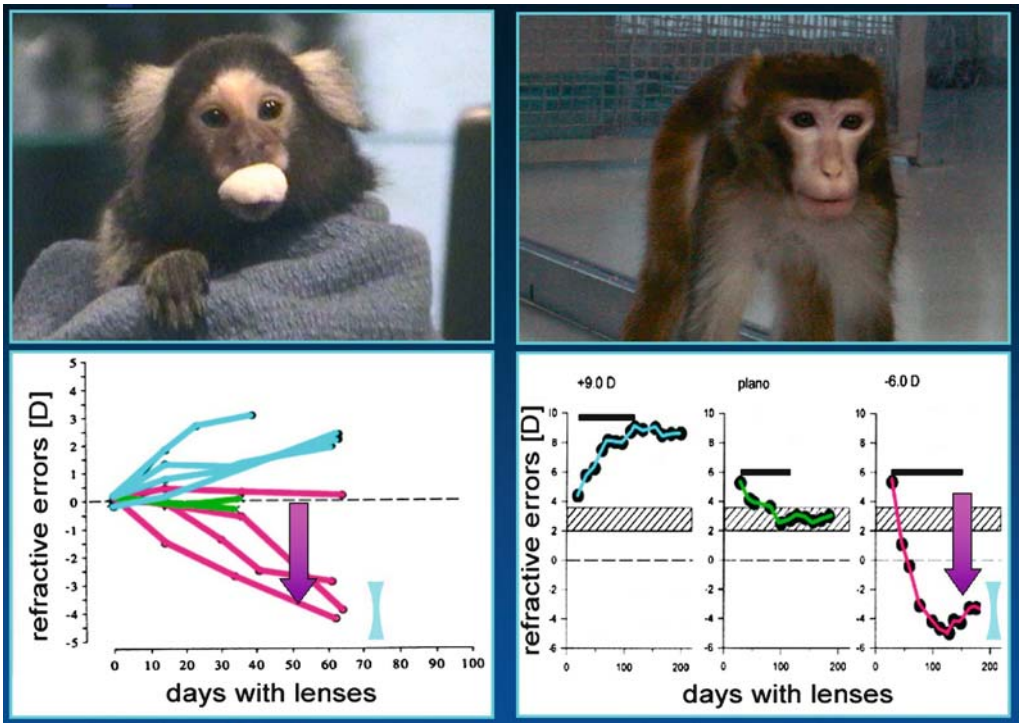

Fig. 1.1. If an emmetropic eye is wearing a negative lens, the focal plane is displaced behind the retina. Several animal models, including marmosets and rhesus monkeys, have shown that the eye develops compensatory axial elongation and myopia. With a positive lens, axial eye growth is inhibited, and a compensatory hyperopia develops (redrawn after [83], marmosets, *left*; [66], rhesus monkeys, *right*)

and the age of the animal [58]. In 1-day-old chickens, up to 20 D can be induced over 1 week of deprivation [77], but only 1 D at the age of 1 year [48]. Rhesus monkeys develop about 5 D on average during an 8-week deprivation period at the age of 30 weeks, but only 1 D at adolescence [68]. Deprivation myopia is strikingly variable among different individuals (range 0–11 D in rhesus monkeys, standard deviations about 5 D [67] (a similar standard deviation is typical also in the other animal models). Although the variability cannot be explained by differences in individual treatment of the animals, it is unclear whether the variability is due to genetic factors. Epigenetic variance could also account for it (R.W. Williams, personal communication, 2003) although it is striking that both eyes respond very similarly despite the lack of visual feedback [57].

Deprivation myopia can be induced in chickens after the optic nerve has been cut [76] and in local fundal areas if only part of the visual field is deprived [78]. Local degradation of the retinal image also produces local refractive error in tree shrews [63]. There are data in both chickens [35] and tree shrews [46] showing that deprivation myopia also can be induced after the ganglion cell action potentials are blocked by intravitreal application of tetrodotoxin, a natural sodium channel blocker. Taken together, the results show that image processing in the retina, excluding its spiking neurons, is sufficient to stimulate axial elongation.

1.2.2.2 Control of Eye Growth by Imposed Defocus

One of the most unexpected results of the chicken studies was that imposed defocus was compensated even if the connection of the eye to the brain was disrupted by cutting the optic nerve. Even though the baseline refraction of the eye without optic nerve moved to more hyperopia, suggesting general growth inhibition, negative lenses still caused axial elongation, and positive lenses growth inhibition on top of the new baseline refraction [86, 85]. These results suggest that the retina releases factors to control the growth of the underlying sclera. Furthermore, they show that the retina can make a distinction between positive and negative defocus. A retinal control of eye growth is further suggested by the observation that image defocus [6] is compensated in local fundal areas. Since accommodation requires an optic nerve and since accommodation shifts the focal plane, at least in humans and chickens, equally across the visual field, local compensation of refractive errors cannot be explained by a feedback loop that involves accommodation. Any potential effect of accommodation on axial eye growth must be indirect, by changing the focus of the retinal image.

Experiments with lenses after optic nerve section have not yet been conducted with monkeys. Therefore, it cannot be safely concluded that monkey eyes compensate imposed defocus based on a purely retinal mechanism. At least, it has already been shown [90] that the transcription factor Egr-1 in the monkey retina is regulated by the sign of imposed defocus, similar to the chicken [4, 12, 65].

1.2.3 What Is Known About the Retinal Image Processing That Leads to Refractive Errors?

Ignoring accommodation (which is, at least, apparently not necessary), to determine the sign of the refractive error of the eye, the retina could compare the focus for different viewing distances. However, additional information must be available on the dioptric distance of the viewing target. The other option is that the retina has a mechanism to measure the vergence of incoming rays instantaneously. Even though this idea seems hard to accept, experimental evidence is clearly in favor of this hypothesis.

Chickens that are individually kept in the center of a large drum so that they have only one viewing distance can compensate the power of lenses of either sign. In this case, lens powers were chosen so that the far point of the eyes was either behind or in front of the walls of the drum by the same dioptric amount of 12 D. In addition, accommodation was suppressed by cycloplegic agents. If the retina would only measure image sharpness and contract, all these treatments should have led to deprivation myopia. That hyperopia was induced despite massive image degradation, can only be explained by postulating that the retina can determine the sign of defocus [55]. It is quite impressive that the growth inhibition signal overwrites the deprivation-related signal for enhanced eye growth. Similar experiments have not yet been conducted with monkeys but, given the similarities among the results from different animal models, it is possible that also the mammalian retina can measure the sign of defocus.

Which image processing algorithms or which optical tricks the retina uses to measure vergence of rays is not clear. The most likely mechanisms are not used or, at least, not required (chromatic aberration, spherical aberration, astigmatism): Chickens compensate spectacle lenses equally well in white or monochromatic light [57]. They also compensate lenses at different illuminances and, hence, different pupil sizes and amounts of spherical aberration [38]. They compensate the spherical refractive errors even in the presence of extreme astigmatism [36]. Recent observations in chickens suggest that the sign of defocus detection is no longer possible if the chicks were exposed to the same visual experience under anesthetized conditions (M. Bitzer, personal communication, 2004).

Both chickens [7] and humans (e.g., [81]) can rapidly adapt to low image contrast. Since this adaptation is spatial frequency-specific, contrast adaptation can also partially compensate for the visual effects of defocus [37]. As a result,

visual acuity can increase over time when defocus is maintained – a well-known experience of myopic subjects who take off their glasses. The increase in acuity is not based on refractive changes and there are no biometric changes in the eye [26]. It has also been shown that contrast adaptation is possible both at the retinal and cortical level [19]. A comparison of contrast adaptation levels at different spatial frequencies could be used as a measure of the amount of defocus over time [20]. Therefore, it has been speculated that more contrast adaptation at high spatial frequencies may indicate the presence of defocus, and that this could be a signal that could trigger axial eye growth [7]. It is clear, however, that contrast adaptation does not carry any information on the sign of defocus. Rather, it should be related to the retinal mechanisms that cause deprivation myopia.

1.2.4 How Long Must Defocus Persist to Induce Changes in Eye Growth?

The kinetics have been extensively studied by Winawer and Wallman [87] in chickens. Their finding that the temporal summation of defocus is highly nonlinear was not totally unexpected, as this was indicated by the experiments of Schmid and Wildsoet [64], who showed that the response of refraction to brief periods of normal vision in lens-reared chicks varied greatly with the sign of the lens. Winawer and Wallman found that multiple daily periods of defocus produce much larger changes in eye growth than one single period of the same total duration. If the single periods of lens treatment were shorter than 20 s, the lenses had no effect on eye growth. The most compelling result was, however, that the effects of positive and negative lenses did not cancel each other out: if negative lenses were worn all day, but were replaced with positive lenses for only 2 min, four times a day, the refractive state shifted still in the hyperopic direction [91]. Similarly, if monkeys wore negative lenses all day except for 1 h, the refraction remained in the range of normal animals [25]. These results suggest that the eye normally has a built-in protection against myopia development. It is also striking that the time constants for inhibition of deprivation or negative lens-induced myopia by interruption of treatment are very similar among different animal models [70]. A difference between chicks and monkeys was that interruption of negative lens wearing with positive lens wearing did not inhibit myopia more than interruption without lenses. However, the positive lenses used in the rhesus monkeys were +4.5 D and may have been too strong, given that the linear range of compensation is narrower in monkeys, compared to chickens.

1.2.5 What Is Known About the Tissue Responses and the Signaling Cascade from the Retina to the Sclera?

Once the retina has detected a consistent defocus, the release of yet unknown signaling molecules is altered, which changes the growth rate of the underlying sclera. The cellular candidates for the release of growth-controlling messengers are the amacrine cells, although this is not proven [12]. The signaling molecules reach the retinal pigment epithelium (RPE), where they bind to receptors to trigger the release of secondary messengers at the choroidal side of the RPE. It is less likely that they are transported through the tight junctions of the RPE to diffuse toward the sclera. Wallman et al. [80] were the first to observe in chickens that the choroid rapidly changes its thickness in such a way that the retina is moved closer to the focal plane (thinning when the image plane is behind the photoreceptor layer and thickening when it is in front). In chickens, this mechanism can effectively compensate for considerable amounts of refractive errors (up to 7 D), but in monkeys, where it has also been observed (marmoset: [44, 45]; rhesus monkey: [22]), it has only a minor effect in the range of a fraction of a diopter. Interestingly, the molecular signals for changes in choroidal thickness are different from those that regulate the growth of the sclera (summarized by Wallman and Winawer [79], p 455).

The biochemical nature of "the" retinal growth signal is not yet resolved. Several trans-

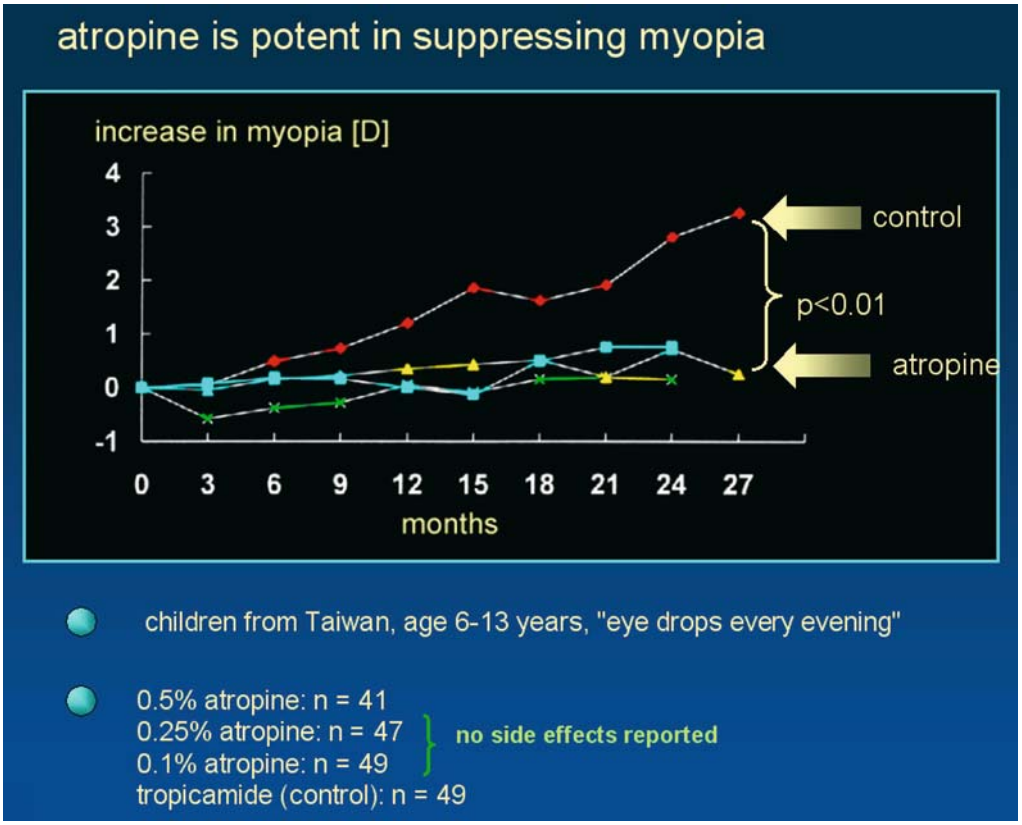

Fig. 1.2. Inhibition of myopia development in three groups of children in Taiwan, who received eye drops every evening with different concentrations of atropine. Note that all concentrations used inhibited myopia. In the case of 0.5% solution (*green crosses*), there was even an initial regression of myopia (redrawn after Shih et al. 1999 [62])

mitters seem to play a role. The major candidates are glucagon (which responds in correlation with the sign of defocus in chickens [11, 12]), dopamine (which responds only to image degradation but not the sign of defocus [47,71]), potentially acetylcholine (because cholinergic receptor antagonists inhibit deprivation and lens-induced myopia [72]), but several other transmitters, neuromodulators, and growth factors have also been shown to play a role. In particular, the potential role of acetylcholine has been extensively studied. Although most muscarinic [31] and nicotinic [73] antagonists have an inhibitory effect on myopia development, there are many arguments that the inhibition is not based on specific binding of the antagonist to the respective receptors. The burning question of how cholinergic antagonists can inhibit axial eye growth in a variety of vertebrates (chick: [34,72]; rhesus monkey: [74]; human: for example [62]; Fig. 1.2) remains unanswered.

In the case of atropine, currently still the most effective drug against myopia, at least five different target tissues have been identified (summarized by Wallman and Winawer [79]).

The sclera defines the shape and size of the globe and was therefore always at the center of interest in myopia research. In an attempt to identify targets for pharmacological intervention of myopia, its metabolism has been extensively studied in the recent years (summarized by Wallman and Winawer [79] and [33]). Atropine appears to have a direct inhibitory effect on scleral metabolism [30].

1.3 Can Animal Models Help to Improve the Management of Myopia in Children?

Several questions regarding the management of myopia in children and adolescents cannot be answered from available epidemiological studies. In these cases, the results from animal models may provide helpful suggestions. It should be kept in mind, however, that some children develop myopia even though they had the same visual environment as others, who do not develop myopia. Furthermore, children develop myopia without any treatment with lenses or deprivation, which is definitely a difference to experimental animals.

1.3.1 Undercorrection, Overcorrection, and Full Correction of Myopia

This question is closely related to the question whether the primate retina evaluates only global image sharpness or also the sign of imposed defocus, as previously observed in chickens (see Sect. 1.2.3). If the retina would only respond to the visual deprivation associated with defocus, undercorrection should induce deprivation myopia, with more eye growth (although a myopic or undercorrected eye is still in focus for close viewing distances). It is known that the mechanism for deprivation myopia is actually active in a human eye since ocular diseases that interfere with retinal image sharpness or contrast during childhood cause axial elongation and myopia (i.e., early unoperated cataracts, ptosis, and keratitis). It has not yet been proven that the primate retina can make the sign of defocus distinction to control eye growth in a bi-directional way although, at least, the transcription factor egr-1 in the primate retina has been found to respond to the sign of defocus, just as in chickens (see Sect. 1.2.2.2). If "sign of defocus sensitivity" is present, undercorrection should be beneficial.

Myopia has traditionally been slightly undercorrected with the weakest negative lens that permitted good acuity. However, there are almost no data in the literature to suggest that undercorrection may be beneficial, other than Tokoro and Kabe [75]. This study was not very well designed since treatments were mixed (atropine treatment and undercorrection by 1 D in ten children, compared to 13 fully corrected children). Nevertheless, it was confirmed by Goss [14] that the undercorrected group progressed more slowly (–0.54 D per year) compared to the fully corrected group (–0.75 D per year; $p<0.001$). More recently, a better designed study was conducted in Malaysia [5]. Full correction was given to 47 children (aged 9–13) and 47 children were intentionally undercorrected by 0.75 D. In this study, the fully corrected group progressed more slowly (–0.77 D per year) than the undercorrected group (–1.01 D per year; difference about 20 %, $p<0.01$). In both groups, the average progression of myopia was strikingly high. Although the second study should be more trustworthy, three additional points have to be kept in mind: (1) even with full correction at the time the glasses were prescribed, all children were undercorrected already after a few weeks due to the generally high myopia progression, (2) most myopic subjects have observed that their progression is restarted once new spectacles were prescribed, (3) that undercorrected eyes have a faster progression does not fit with what has been learned from animal models. Undercorrection should have a similar optical effect as wearing a positive lens and, accordingly, should generate a strong inhibitory signal for axial eye growth (see Sect. 1.2.3).

On the other hand, overcorrection would be comparable to wearing an additional negative lens and should stimulate myopia progression. Overcorrection by 1–2 D has been used in 4-year-old children as a potential therapy for intermittent exotropia [28]. However, myopia progression was not enhanced in the overcorrected group (on average about 2.5 D progression over the following 6 years).

Summary for the Clinician

- **In summary, at present, the results from animal models and the human studies are not complementary. It may be necessary to wait for the results of another study on the effects of undercorrection in children, preferably with another racial group, before the correction strategies are adopted**

1.3.2 Reading Glasses

The link between "near work" (such as reading and writing) and myopia has been extensively studied in the recent years ([54]; short summary in [39]), and there is little doubt that the correlation is, on average, highly significant. Although it is not clear what exactly the critical visual experience is, a current hypothesis is that reading imposes a slight defocus to the retina because subjects accommodate too little. In fact, most studies have found a "lag of accommodation" of around half a diopter at a 3-D reading distance [60]. The lag of accommodation places the focal plane behind the retina and could have a similar effect on eye growth as wearing a negative lens. Inspired by this idea, a number of studies have been conducted with reading glasses in children since they should reduce the lag. The first major study from Hong Kong [29] showed a clear beneficial effect of progressive addition lenses with +1.5 or +2.0 D addition, which reduced progression to about half of the progression with single vision lenses (–1.2 D in 2 years). The idea was also tested in a larger multicentric study in the United States, the Correction Of Myopia Evaluation Trial (COMET). This study also showed some beneficial effect of progressive addition lenses (on average, 14 % inhibition of the progression with single vision lenses of about 1 D in 2 years [16]). The authors considered the inhibitory effect as "clinically not significant". However, if the children were clustered according to their lag of accommodation and phorias, the inhibition could rise to almost 60 % in those children who were esophoric, had a large lag of accommodation (>0.43 D) and had less myopia at the beginning of the treatment (>–2.25 D) [17]. It is important also to recognize that the effects of the progressive addition lenses were generally more expressed when myopia was still low. A third major study from Hong Kong (the Hong Kong Lens Myopia Control Study [9]) found only a trend of a beneficial effect of progressive addition lenses, but the effect appeared significant when only children with low myopia were considered.

Summary for the Clinician

- **In summary, these studies demonstrate convincingly that refractive development is also controlled by visual experience in humans (not a trivial statement, after all). They further show that the treatment with reading glasses is worthwhile, at least in a subgroup of children**

1.3.3 Contact Lenses Versus Spectacle Lenses

There is some evidence in the literature that rigid gas permeable (RGP) contact lenses have a beneficial effect on myopia development [50]. A more recent study could not find a difference between contact lens wearers and spectacle wearers (–1.33 vs –1.28 D progression in 2 years [24]). In this study, 105 children aged 6–12 years wearing contact lenses were compared with 192 children wearing spectacles. Because this is a potentially important issue, another major study is underway (the CLAMP study, Contact Lens and Myopia Progression study). Why myopia should be inhibited with hard contact lenses, but not with soft ones is also an interesting question [13]. It is clear that hard contact lenses flatten the cornea for several days, and that this mimics a reduction of myopia. Therefore, vitreous chamber depth measurements are necessary to confirm that there was really growth inhibition.

The observation from animal models that refractive state is locally controlled, also in the peripheral retina (see Sects. 1.2.2.1 and 1.2.2.2), suggests another possible explanation: spectacle lenses could produce more hyperopic refractions in the peripheral retina than hard contact lenses and this could stimulate more eye growth. Until now, only very limited data have been published on the peripheral refraction of human eyes with hard contact lenses compared to spectacle lenses [61]. This study found that, on average, there was 0.43 D more hyperopia at 22° off-axis with spectacle lenses, compared to hard contact lenses (p=0.026). The question merits further studies in a larger sample.

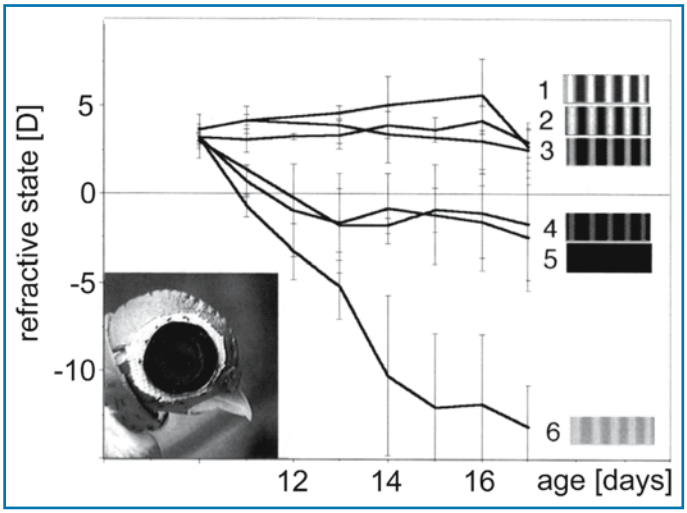

Fig. 1.3. Lowering the retinal image brightness in the chick eye by light neutral density filters has no effect on refractive development as long as the filters are weak (*1* no attenuation, *2* 0.5 log units, *3* 1.0 log units). If the filters are more dense (*4* 2.0 log units attenuation) some myopia develops, similar to when the filters are completely black (5). However, frosted diffusers that attenuate the light only a little (0.38 log units) cause much more myopia (*6*). This result suggests that low retinal image brightness interferes with eye growth. Furthermore, if the chicks are kept in low light (2.0 log units less than controls), even clear occluders cause some myopia, suggesting that eye growth becomes more sensitive to minor image degradation. Redrawn after [10]

Summary for the Clinician

- **The evidence for an inhibitory effect of hard contact lenses on myopia development is mixed. It is advisable to wait for the results of the CLAMP study**

1.3.4 Illumination, Reading Distance, Computer Work Versus Reading Text in a Book

It is surprising that there are only studies from chickens to determine whether ambient illuminance has an effect on myopia development. It was found that refractive errors imposed by spectacle lenses are similarly compensated over a wide range of illuminances (see Sect. 1.2.3). Therefore, these experiments provide no evidence that reading at low light may represent a risk factor. Only Feldkaemper et al. [10] have studied whether reduction of retinal image brightness by covering the eyes with neutral density filters can induce deprivation myopia. Refractive development was not altered if the filters attenuated the ambient light (illuminance 400 lux) by less than 2 log units. With darker filters, however, the refractions became more myopic, although not as myopic as with frosted eye occluders that degraded the retinal image, but attenuated light only by 0.38 log units. Furthermore, when the animals were placed in dim light (2.0 log units lower than controls) they did not become myopic without eye occluders but, even "clear" filters (denoted as "1" in Fig. 1.3), caused some myopia. These results suggest that eye growth becomes more sensitive to minor image degradation when the retinal image brightness is reduced (Fig. 1.3).

A possible reason why this could happen is that both retinal image brightness and retinal image contrast and sharpness reduce the release of dopamine in the retina [10], and dopamine release has been shown to have an inhibitory effect on eye growth [47]. Even though these observations are from chickens, they suggest that reading (which also represents a minor image degradation due to the lag of accommodation) might be more myopigenic at poor illumination.

One would expect that reading distance is also important because the lag of accommodation increases with decreasing target distance. Pärssinnen and Lyrra [49] studied 238 Finish school children at 10 years of age and found that myopia progression was higher in those children who read at 20 cm distance than in those reading at 30 cm distance. However, it should be kept in mind that this relationship need not be causal – it could be that children with higher myopia progression also have the habit of reading with shorter target distances.

There is no evidence that a computer screen has a different effect on myopia progression as a text printed on paper. It is likely, however, that extended work on the computer causes myopia due to the constantly short viewing distances. Several studies have come to this conclusion [41]. Given the extreme growth rates of the computer market in the Far East, it appears likely that the rapid increase in myopia in schoolchildren is, in fact, related to computers. Everybody who has children realizes how fascinating computer games are for them, compared to books. There is no doubt the "dose" of near work is greatly increased with computers.

Summary for the Clinician

- **That reading at poor illumination increases the risk of myopia development is only suggested by experiments in chickens. Despite the lack of other evidence, it is still advisable to use appropriate illumination. Reading distance is a critical factor and reading should occur at sensible distances (i.e., 30 cm). There is no evidence that computer work is more myopigenic than reading a book at the same distance, but the computer is more attractive, increasing the "dose" of near work**

1.3.5 How Long Must the Near Work Be Performed to Induce Myopia?

Initially, the amount of near work was quantified in "diopter hours" (amount of accommodation × duration in hours). However, there was an inherently low correlation between myopia progression and the amount of near work, as measured in diopter hours [43], although significant correlations were achieved because of the large numbers of samples already in the early studies (i.e., 793 children [88]). A large study on the relationship of near work and myopia in 1,005 school children in Singapore, 7–9 years old [54], showed that axial eye length was correlated to the myopia of the parents but also to the numbers of books that were read per week. There was a significant increase in myopia when two books were read vs when one book was read, but only in those children whose two parents were myopic. One possible explanation for the relatively low correlation between near work and myopia is that the exact behavioral pattern during reading may be important. It was already suggested by Winawer and Wallman [87] that diopter hour may not the best unit to predict myopia from near work.

Summary for the Clinician

- **If the observations in animal models (see Sect. 1.2.4) are applicable to human myopia, interruption of reading for only short periods, and looking at a distance, should effectively inhibit the growth signal for the eye. More research is necessary in the monkey model and in children to find out whether temporary wearing of positive lenses could further strengthen this inhibitory signal for axial eye growth**

1.3.6 Night Light, Blue Light

Based on the observation that the ocular growth rhythms are disturbed during development of deprivation myopia in chickens [82, 44], whether diurnal light rhythms might interfere with myopia development in children was tested. In the initial study [52], a high correlation between exposure to light during the night and myopia development was found. Later studies [15, 89] could not confirm this relationship and one possible explanation was that myopic parents had the lights on at night more frequently. The higher incidence of myopia in their children