Why Do Only Some Hyperopes Become Strabismic?

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Children with hyperopia greater than +3.5 diopters (D) are at increased risk for developing refractive esotropia. However, only approximately 20% of these hyperopes develop strabismus. This review provides a systematic theoretical analysis of the accommodation and vergence oculomotor systems with a view to understanding factors that could either protect a hyperopic individual or precipitate a strabismus. The goal is to consider factors that may predict refractive esotropia in an individual and therefore help identify the subset of hyperopes who are at the highest risk for this strabismus, warranting the most consideration in a preventive effort

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Amblyopia and strabismus acquired during infancy and early childhood can permanently disrupt a child's visual development.^{1–5} There is currently significant interest in screening for these disorders with the hope that diagnosis and treatment will allow children to achieve their full potential.^{6,7} There is also significant interest in screening at younger ages in an attempt to prevent the vision loss associated with these conditions,⁸ for example, by manipulating visual experience with early spectacle correction.^{9–11} The goal of prevention is supported by (1) prospective studies of animal models demonstrating that abnormal visual experience can lead to abnormal development of synaptic circuitry in visual cortex,^{12–18} and (2) the hypothesis that providing “normal” visual experience to human infants will prevent the development of clinical abnormality.^{9–11}

This concept of prevention is particularly appealing for forms of esotropic strabismus associated with accommodative effort. Accommodative effort is thought to precipitate a convergent misalignment of the eyes as a result of increased hyperopic refractive error (an increased accommodative demand) and/or increased accommodative convergence to accommodation (AC/A) ratio (excessive accommodative convergence).^{19,20} If the accommodative effort and its coupled impact on vergence could be relieved at an early age, it is appealing to think that the convergent misalignment and onset of amblyopia could be prevented.

The prevalence of esotropia between 6 and 72 months of age is estimated to be between 1% and 2% for white, African American, and Hispanic populations^{21–23} (see also Ref. 24). Prevalence in Asian populations appears to be lower, as less than 0.1% of 6- to 72-month-old Singaporean Chinese and Japanese children^{25,26} and 0.28% of Japanese 6- to 12-year-old children are esotropic.²⁷ Over half of all reported cases of esotropia are considered to be related to accommodative effort.^{28,29} Therefore, prevention of esotropia related to accommodative effort would likely impact on the order of 1% of the US population.^{28–30}

Refractive esotropia, with a typical AC/A ratio and increased levels of hyperopia, has a peak onset at 2 to 3 years of age¹⁹; therefore, there is a period of postnatal development during

which a preventive approach could theoretically be applied. Around 5% of white, African American, and Hispanic 6- to 9-month-old infants have hyperopia greater than +3.5 D in at least one meridian,^{31–34} and infants who do not lose this hyperopia through emmetropization^{31,35,36} are at greatest risk for the strabismus and secondary amblyopia. For example, in the large-scale studies by Ingram et al. and Atkinson et al. measuring incidence of esotropia, 15% to 25% of infant hyperopes (with refractive error [RX] >+3.5 D) developed esotropia by 4 to 5 years of age (Fig. 1),^{9–11} with no analysis provided about race (all of these studies took place in England). In looking at refractive error in more detail, Birch et al.³⁷ found that the prevalence of accommodative esotropia in children 1 to 8 years of age increased for larger values of hyperopia: 12% for RX +2 to +3 D, 38% for RX +3 to +4 D, 73% for RX +4 to +5 D, and 60% for RX greater than +5 D (see also Ref. 22).

In the first few months after birth, infants have an average hyperopic refractive error of +2.2 D (SD ± 1.4).^{31,35,38} Through a process termed emmetropization, most of them lose the bulk of their hyperopia within the first year after birth.^{31,35,38} Mutti et al.,³¹ for example, found that 24.8% of 3-month-old infants had a hyperopic refractive error greater than or equal to +3.0 D compared to only 5.4% at 9 months of age. Emmetropization is believed, based on studies of animal models, to occur via an active mechanism by which defocus drives growth of the eye.^{39–42} By 4 years of age, mean hyperopic refractive error is approximately +1.1 D (SD ± 0.85).^{34,35} Some infants, however, do not emmetropize and maintain a large refractive error (RX > +3.5 D) into their second and third year of life.^{9–11} It is unclear why these infants do not emmetropize; and these individuals, as a result of their large refractive error, are at a greater risk for refractive esotropia.^{9–11,37}

Beyond refractive error, race, and ethnicity, family history also plays a role, as between 23%³⁷ and 67.3%⁴³ of children with accommodative esotropia have an affected first-degree relative by parental report (see also Ref. 44). Birch et al.³⁷ found that 91% of their subjects had at least one affected relative when more distant relationships were included. No specific pattern of inheritance or genetic locus has been identified to date, however.^{45,46} When examining 115 siblings of patients

FIGURE 1. Incidence of esotropia. Onset was between 9 months and 4 years for Atkinson et al., program 1¹¹; 9 months and 5½ years for Atkinson et al., program 2⁹; and between 6 months and 3½ years for the Ingram et al. program.¹⁰

with accommodative esotropia, Shah, Torner, and Mehta⁴⁷ noted a high prevalence (43%) of strabismus and/or refractive error, and both Aurell and NorrSELL⁴⁸ and Abrahamsson et al.⁴⁹ found the highest rates of esotropia in subjects with both higher hyperopia and a family history of strabismus.

Birch et al.³⁷ and Weakley and Birch⁵⁰ also note an increased risk for a deviation in hyperopic children with anisometropia of a diopter (D) or more, particularly in those with lower amounts of hyperopia.

Classically, esotropia associated with hyperopia is considered to result from an increased accommodative response, due to the hyperopia, that drives excessive convergence via the neural coupling between the two motor systems.^{51,52} Under this hypothesis, compliant use of preventive spectacle correction should prevent the strabismus. Atkinson and Ingram and their colleagues performed controlled prospective population-based studies that looked at the impact of early hyperopia correction on the incidence of strabismus and amblyopia.^{9–11,53–55} Partial hyperopic correction was given based on the hypothesis that it would provide “normal” visual experience indirectly through a more normal accommodative demand. Unfortunately, the results of these studies have been somewhat ambiguous (see Fig. 2). The corrections reduced the prevalence of severe amblyopia at 3 to 4 years of age,^{9,10,54} but the strabismus data are less conclusive. Ingram’s group found the prevalence of strabismus at 3½ years of age to be the same in the treated and untreated hyperopic groups (24% with glasses and 26% without glasses¹⁰), while Atkinson’s group found a reduction in the prevalence of strabismus at 4 years of age in the treated group in their first program (6.3% with glasses and 21% without glasses⁵⁴) but no reduction in prevalence for the treated group in their second program (20% with glasses and 11% without glasses⁹). These trials of spectacle correction had somewhat different protocols and therefore their interpretation is complex; it is, however, clear that they did not result in a dramatic and consistent prevention of strabismus (see also Ref. 56).

Only a proportion of the hyperopes in the large-scale studies by Ingram et al. and Atkinson et al. developed the strabismus *with or without* optical correction. *Why might*

some uncorrected high hyperopes develop strabismus while others with matched refractive error remain aligned? Why might this happen even in hyperopes given optical correction? In exploring these questions there are a number of factors beyond refractive error and family history that may be considered. In the context of the classical explanation for the strabismus, anything that drives excessive convergence would put an individual at risk.^{57–60} The goal of this review is to consider additional oculomotor factors that may help predict refractive esotropia in an individual and therefore help identify the subset of hyperopes who are at the highest risk for this strabismus, warranting the most consideration in a preventive effort.

Normal visual experience during development is dependent upon both the accommodative and vergence motor systems in that they control retinal image quality and correspondence, respectively. The two systems are also neurally coupled; an effort to accommodate results in a convergence response (i.e., accommodative convergence), and an effort to converge leads to an accommodation response (convergence accommodation). This coupling facilitates the achievement of single and clear vision in adults.^{61–63} Such coupling appears advantageous when the accommodative and vergence demands are similar; but its benefit during development or in the presence of high hyperopia is less clear, as there can be a large discrepancy between vergence and accommodation demands. Infants typically have a large accommodative demand because, as a group, they have the highest levels of uncorrected hyperopia and need to accommodate more to overcome their refractive error.^{31–34} In contrast, they have a small angular vergence demand because their interpupillary distance is narrow, and as a result, the angle of rotation needed to converge to a target is smaller than in older children and adults (see Fig. 3). In the simplest sense, one might predict that newborns would be at the highest risk for refractive esotropia because they have the greatest potential for increased accommodative effort to drive an excessive rotation of the eyes that exceeds their reduced angular vergence demand. However, as noted above, refractive esotropia frequently does not manifest until the preschool years.¹⁹ In discussing how some hyperopes avoid strabismus,

FIGURE 2. Effect of prescribing glasses for higher hyperopia on the incidence of esotropia.^{9–11} Noncompliant hyperopes were the individuals who wore glasses less than 50% of the time.

we will also ask *why the youngest infants escape this strabismus and older patients go on to decompensate*.

The development of the accommodation and vergence systems and their coupling are reviewed in the following sections, in the context of the questions posed above; then the questions are addressed directly in a more specific discussion of refractive esotropia.

The Development of Accommodation

Do young infants avoid strabismus because as a group they do not accommodate accurately, and therefore do not drive accommodative convergence? A number of research groups have looked at the development of accommodative accuracy to static stimuli during infancy.^{64–69} The consensus has been that before 3 months of age, infants wearing no optical correction tend to overaccommodate for distant targets and underaccommodate for near, implying a reduced gain in their response function. Banks,⁶⁴ for example, found that the relative changes in accommodative response to targets at positions of 1, 2, and 4 D became more accurate with development, from response slopes of 0.51 at 1 month to 0.75 at 2 months and 0.83 at 3 months, as compared with 0.93 in adults. In agreement, it does not appear that accommodative accuracy changes dramatically after 3 months of age; accommodative response gains were not found to change systematically between 3 months and 46 years of age for typical near viewing distances.⁷⁰ By 3 months of age, most infants also have relatively small accommodative lags for targets at distances between 50 and 25 cm,^{38,71,72} and therefore it is not the case that young infants simply do not generate accommodation responses.

Is there an age at which accommodating to near targets requires the maximum accommodation individuals can generate, thereby challenging the system? There are few estimates of young infants' maximum amplitudes of accommodation, and these results can only represent a lower estimate because it is not possible to confirm that a young child was performing at their maximum capability. Maximum accommodative amplitudes of 7 to 15 D have been reported for 2- to 3-year-olds.^{73,74} This level is then proposed to either decrease linearly with age from 2 to 15 years⁷³ or remain constant until approximately 20 years of age, after which it decreases.⁷⁴ Woodhouse et al.⁷⁵ also noted a median maximum amplitude of >11 D in typically developing 7- to 11-year-old children. Thus it is certainly possible that a higher hyperope might reach his or her maximum amplitude of accommodation when attempting to focus at a short viewing distance. Further studies are required to determine whether there is a significant decrease in the maximum amplitude with age, which might permit a young infant to accommodate comfortably to a near distance but cause a 2- or 3-year-old to struggle and generate excessive effort.

A number of more recent studies, with the development of video-based photorefractive, have found that the dynamics of the infant accommodative response are also relatively accurate.^{76,77} By 3 months of age, most infants are able to initiate an accommodative response within half a second of a change in target distance and to adjust the velocity of their responses to the velocity of the target movement.⁷⁷ They are also able to maintain a steady-state response with a root mean square (RMS) fluctuation of 0.3 D, a factor of only two greater than the 0.15 D RMS recorded from the adult subjects⁷⁸ (see also Refs. 79–81) and very close to the 0.26 D RMS recorded from 3- to 9-year-old children by Anderson et al. using similar equipment.⁸² Three-month-olds also generate a response in binocular viewing to a stimulus motion of less than 0.5 D, as compared with less than 0.25 D recorded from adults.⁸³ These results all

FIGURE 3. Schematic illustration of the change in accommodation and vergence demands during postnatal visual development. The infant has a narrower interpupillary distance leading to a smaller angular vergence demand, and a more hyperopic refractive error leading to a greater accommodative demand than found in adults.

suggest that typically developing 3-month-old infants are able to initiate and control the accommodative responses necessary to avoid chronically high levels of retinal image blur that could result from their hyperopic refractive error and typical changes in target distance.⁸⁴ Thus it does not appear that the later onset of refractive esotropia can be attributed to basic developmental maturation of accommodative accuracy; even 3-month-old infants typically appear capable of exerting significant amounts of accommodation to near targets.

Do typical behaviors of infants and young children change such that young children use their accommodative system more at the age of onset of the strabismus? The typical relatively late age of onset of refractive esotropia after infancy does not appear to be due to a lack of near activity during infancy. Infants frequently explore novel objects both visually and manually.^{85,86} In particular, episodes of object mouthing or finger manipulation are often coupled with or followed by visual exploration^{86,87}; and it has been found that young infants, 4 to 5 months of age, spend 33% of their time visually exploring objects.⁸⁶ There does, however, appear to be a shift between 1 and 3 years of age in which focused attention increases (where focused attention is defined as effortful concentration coupled with visual fixation) and distractibility decreases.^{88–91} For example, the mean duration of an episode of focused attention increased with age from 3.3 seconds at 1 year to 5.4 seconds at 2 years to 8.2 seconds at 3.5 years of age.⁸⁹ The duration of the longest episode of focused attention also increased between 2 and 4 years of age from 16.6 seconds (SD $\pm$ 7.7) at 2.5 years to 27.6 seconds (SD $\pm$ 14.1) at 3.5 years of age (with no change between 3.5 and 4.5 years of age).⁸⁹ Such an increase in focused attention with age is likely driven by cognitive development as type of play changes from

TABLE. Baseline Tonic Accommodation Position (D) in Myopes, Emmetropes, and Hyperopes

	Age	Baseline Tonic Position, D		
		Myope	Emmetrope	Hyperope
Gwiazda et al., 1995	6.5–16.5 y	0.30	0.75	0.94
Rosner and Rosner, 1989	6–14 y	1.36	1.54	1.73
Zadnik et al., 1999	6–15 y	1.02	1.92	2.25
Maddock et al., 1981	Adults	0.74	0.98	1.30

exploration of, and habituation to, novel object features to more open-ended activities like toy construction and problem solving.^{89,92–94} An increase in the duration of focused attention in the period from 1 to 3 years of age potentially provides an explanation for refractive esotropia appearing in this age range. More research is needed to further evaluate this hypothesis, however, as strabismus is noted to develop over a relatively wide range of ages from approximately 6 months to 6 years. The question of individual differences in accommodative responses is discussed further in the section on development of refractive esotropia.

Which cues can be used to drive an accommodative response? Heath⁹⁵ described accommodative responses in terms of four components: reflexive (blur-driven), proximal (sense of “nearness”), tonic (resting or baseline), and neurally coupled vergence accommodation, with blur as the error-correcting cue driving a response (see also Ref. 96). As reviewed below, there is evidence that these components are present in early infancy and therefore that they could play a role in normal and abnormal visual development. They are proposed to have differing impacts on accommodative convergence and therefore have the potential to influence the clinical outcome for a young hyperope.

Blur is considered to be the primary cue driving accommodation in adults,^{95,97} and, through a feedback loop, is proposed to drive correction of accommodative errors resulting from the other components of the response. An individual's blur sensitivity, or depth of focus, at any moment in time will depend on both the sensitivity of the visual system to blur and the spatial content of the stimulus. For example, it has been demonstrated that adult accommodation responses are reduced and less accurate to low spatial frequency targets (<5 cycles per degree [cpd]) than high spatial frequency targets (between 10 and 20 cpd).^{95,98} Infants are sensitive only to low spatial frequencies,^{99–103} which would affect their blur sensitivity. For example, Green, Powers, and Banks¹⁰⁴ developed an estimate of infant blur sensitivity, or depth of focus, incorporating pupil size and visual acuity. They modeled the limits imposed by both the extent of a blur circle on the retina and the neural visual system's ability to encode high-contrast retinal image content. They estimated the response slopes or gains of the infant accommodation system at 1 and 3 months of age, finding values comparable to the empirical slopes of Banks⁶⁴. Slopes or gains were predicted to be between 0.2 and 0.6 at 1 month and between 0.8 and 0.9 by 3 months of age, suggesting that developmental improvements in accommodative accuracy may be related to improving sensitivity to blur over this same time period.

As noted above, proximity is one's abstract sense of nearness, which has been shown to drive accommodation in adults.^{105–108} Potential cues driving a sense of nearness include looming (motion in depth) and pictorial cues (e.g., occlusion, relative and familiar size, size constancy, linear and motion perspective, and texture gradients). This information can drive blinking,^{109–111} head movements,^{109–113} preferential looking,^{114–117} and reaching behaviors^{118–123} in infants. The age

of onset of sensitivity to proximity during infancy has been debated, however, in part because these responses to proximity (e.g., reaching) will become apparent only once the motor response has come online. For example, infants demonstrate preferential looking to pictorial cues within the first 4 to 5 months of age,^{114–117} while preferential reaching responses (to a closer target, as specified by pictorial information) appear at approximately 5 to 7 months of age.^{118–123} While it is unclear at what age infants can start using proximal cues to drive accommodation, it does appear that they are sensitive to looming information by 2 to 4 weeks of age as evident in their blinking responses.^{109–112} Blinking may reflect an immature avoidance response to an approaching visual stimulus, and this signal could in theory be used to guide early accommodation responses. Preliminary evidence of proximity-driven accommodation in infants has been provided by Currie and Manny,⁶⁷ who found that 1.5 ($n = 4$)- and 3 ($n = 3$)-month-old infants generated accommodation responses to a diffuse white light at 25 cm, with minimal other accommodative cues available. The role of proximal accommodation in refractive esotropia depends on its capacity to drive accommodative convergence.^{107,124} If this component of accommodation does not drive accommodative convergence in infancy, it could help overcome hyperopia without leading to excessive convergence—a benefit. If it does drive the coupling to vergence, it could contribute to the overconvergence and strabismus.

Even less is known in early development about the third of Heath's components, tonic accommodation. When accommodation and vergence are made fully “open loop” by removing both blur and disparity feedback, the responses return to a baseline resting point—termed tonic accommodation and tonic vergence.^{95,125} Tonic accommodative activity may be advantageous, as it does not appear to drive vergence via the accommodative-convergence coupling in adults.^{57,60,126} This component responds relatively slowly to compensate for sustained accommodative demand, and therefore it is an appealing candidate for a mechanism by which infants could accommodate to overcome their ongoing hyperopia and yet not drive the excessive vergence. Aslin and Dobson¹²⁷ demonstrated that the tonic system is active in infants by examining their responses in the dark and therefore in the absence of feedback about blur and disparity. While the limitations of the photorefractive technique (e.g., Refs. 65, 128) may have affected the accuracy of their estimates of the dark focus of accommodation, the researchers found the mean dioptric position to be 1.43 D ($SD \pm 0.25$) in 3- to 12-month-old infants and 1.14 D ($SD \pm 0.04$) in adults (this difference was not statistically significant). Given that infants are typically hyperopic, this indicates that their total accommodation response in the dark was greater than found in the adults. Other studies of hyperopic school-aged children and adults ($RX > +0.75$ D) have found that hyperopic participants had an increased tonic accommodative response when compared to emmetropes and myopes (see Table).^{129–132} There were, however, inconsistencies across studies with regard to the

use of habitual optical correction or new correction during testing, and the results need to be interpreted carefully in this context. If present, however, an increased tonic response during infancy or early childhood could be either an experience-dependent adaptation to an individual's current refractive error or, in the absence of this active adaptation, a common developmental immaturity across all individuals. If hyperopes consistently demonstrate an increased tonic response even in the presence of full distance optical correction, these data would suggest that the individuals are not adapting to their current visual demands.

One metric that is commonly used to assess the tonic system is its adaptation to a change in sustained visual demand,^{133–136} for example, the change in tonic response after an individual transitions from viewing in the distance to a period of prolonged near work. This form of adaptation would also be consistent with experience-dependent active adaptation to current visual demands, as described above. Adaptable tonic responses could theoretically play a role in compensation for changing demands with growth of the head and change in refractive error. If active during infancy and early childhood, these adaptive responses could protect an individual from the overconvergence and esotropia driven by accommodation, as discussed earlier. In fact, abnormal adaptation of tonic responses has been implicated in some binocular vision problems in adults.⁵⁷ Interestingly, older hyperopic children (7–16 years of age) have shown a smaller adaptive shift in their accommodation response (0.24 D) following prolonged fixation on a stimulus than have emmetropic children (0.68 D).¹²⁹ If this smaller adaptive shift were consistent in young hyperopes, it would suggest that the resting or tonic response may not be as dynamic as in emmetropic children. This could be evidence of a number of things: an inability to adapt perhaps, or of having reached a maximal tonic response, or of a timescale difference in which a longer period of sustained accommodation is required in order to adapt.

In the context of strabismus, when baseline tonic accommodation responses in fully optically corrected hyperopic children (mean age 9.6 years, range 5–15 years) with and without accommodative esotropia were compared, children with esotropia had a closer dark focus (2.7 D relative to their hyperopic far point) than those without (1.1 D) despite similar refractive errors.¹³⁷ This is *inconsistent* with the idea that increased tonic responses would be protective against strabismus in the simplest sense. If tonic responses were used, without driving the coupling, to overcome hyperopia in nonstrabismic patients, one would predict that these nonstrabismic patients would have higher tonic responses. The limited amount of data to date, in combination with the observation that hyperopic children do not have adaptable tonic accommodation, suggest that tonic accommodation does not have a simple protective role in a patient's clinical outcome, although very little is known about its role in infant hyperopes.

The final component of Heath's classification is vergence accommodation. This is the accommodative response driven by the coupled vergence motor system. In the clinic, the gain of the interaction is described using the ratio of convergence accommodation to convergence (CA/C). Current evidence suggests that vergence accommodation is active soon after birth.¹³⁸ Bobier et al.¹³⁸ measured the CA/C ratio of 3- to 6-month-old infants using a highly blurred target to remove feedback about small changes in blur (blur open-loop) while they drove vergence with prisms to elicit vergence accommodation. They found decreasing stimulus CA/C with increasing age (0.73 D/meter angles [MA] in infants vs. 0.25 D/MA in adults), suggesting that the accommodative demand due to hyperopia in early infancy might be at least partially relieved by

an increased coupled accommodative response driven by the vergence system (high CA/C ratio). The impact of this coupling and also the inverse, accommodative convergence, will be discussed in greater detail below.

To summarize, in the context of the development of refractive esotropia, the literature suggests that typically developing infants should be capable of maintaining an accommodative response within approximately 0.75 D of a near stimulus from the age of 3 months. This amount of error is considerably less than the defocus that higher hyperopes would experience if they did not accommodate. At this age, infants also have the potential to use the different response components defined by Heath⁹⁵ to achieve this response. Their use and weighted combination in full-cue naturalistic conditions is poorly understood, however. A key question is to ask how these individual components are driving the coupled accommodative vergence, in the context of the classical excessive accommodative convergence model of refractive esotropia. It may be that the relative balance between these components changes with age, allowing young infants to avoid the strabismus. Furthermore, the effect of these components of accommodation on coupled vergence may help us better understand why only some individuals with high hyperopia develop the strabismus, even in cases with optical correction.

The Development of Vergence

Accurate vergence is necessary for single vision in a typical binocular visual system. Infants are able to fixate a visual stimulus with both eyes as early as a few days after birth¹³⁹; however, vergence responses measured at 1 month of age tend to be less accurate and more variable than those recorded between 2 and 4 months of age.^{140–142}

Vergence responses to dynamic targets improve between 1 and 3 months of age,^{142,143} in terms of both direction and accuracy. Overall, the response accuracy is believed to fall close to adult ranges at around 3 months of age,^{68,140} and there do not appear to be any systematic changes in vergence gain between 3 months and 46 years of age for typical near distances.⁷⁰ It is therefore assumed that 3-month-olds do not experience diplopia (double vision) routinely, although their percept can only be inferred.^{142,144,145} Tondel and Candy¹⁴⁶ demonstrated that vergence latencies are typically less than a second between 6 and 23 weeks of age (with no age trend), providing evidence that the system is also quite responsive in the time domain. Some infants also demonstrated adult-like latencies of less than 0.5 seconds by 7 to 8 weeks of age with the instrumentation used.¹⁴⁶

When the information from the two eyes is not fused, a percept of diplopia may result, or the information from one eye may be suppressed. Inaccurate binocular eye alignment in the youngest infants^{139,142,143} implies either that they are able to achieve sensory fusion over larger angular offsets (larger Panum's fusional area), or that they are experiencing some form of altered percept such as diplopia, rivalry, superposition, or monocular suppression¹⁴⁷ (but see Refs. 148, 149). Our inability to access infants' percepts makes this a hard topic to explore. Two groups have noted disrupted sensory binocularity in patients with recent-onset or intermittent accommodative esotropia^{13,37,150–152} and have suggested that the disruption could in fact have contributed to the development of the refractive esotropia. If it does indeed precede the strabismus, the deficit might be primary in nature, possibly congenital, or secondary to some form of prior or current abnormal visual experience—anisometropia, astigmatism, poor accommodative accuracy, or an unstable eye alignment (infantile esotropia in the extreme¹⁵²), for example. The role of sensory binocular performance in the control of vergence

responses prior to the onset of strabismus is, therefore, worthy of further investigation.

Vergence performance can be described using two different units. When considering the accuracy of a response in stimulus space, one might use the MA, as it is equivalent to the diopter (reciprocal of distance in meters); but, given that young infants and children have a narrower interpupillary distance (IPD) than an adult, they require less angular rotation of the eye than an adult to fixate the same location in space (see Fig. 3). Thus, while many vergence measurements are reported in MAs, it is important to also remember that an equal response in meter angles for an adult and an infant is actually a different response in terms of angular rotation of the eyes, in degrees or prism diopters (1 pd is equivalent to 0.57°). This is particularly relevant when one is comparing very young infants to adults, as the difference in IPD is at its largest. This highlights the subtlety required in interpreting the data regarding the development of vergence and the developmental relationship required to achieve registration of the accommodation and vergence motor systems during growth and maturation.

Which cues can be used to drive a vergence response? Maddox¹²⁵ provided the original definitions of the components of vergence responses that were later adopted for accommodation by Heath.⁹⁵ Maddox described disparity, proximal, tonic, and coupled accommodative vergence as the components of a vergence response, with disparity being the error-correcting cue. These components are proposed to form a weighted combination in generating the final motor response, with the classical explanation for refractive esotropia being an excessive accommodative convergence component.

Given that refractive esotropia is typically relatively large and noticeable to an inexperienced observer, the age of onset is relatively well understood. This form of deviation typically starts to develop between 6 months and 6 years of age.¹⁹ Thus, refractive esotropes are able to maintain alignment for some months or years after birth before decompensating into their strabismus, even though the accommodation and vergence systems are active by around 3 months of age. In current models of the vergence oculomotor system,^{59,60,153,154} disparity-driven vergence is the component responsible for correcting any remaining alignment error, based on feedback about retinal image correspondence. Thus, in the classical model of refractive esotropia, disparity-driven vergence would be unable to overcome the remaining misalignment that results from the combination of the other components: proximal, tonic, and the increased accommodative vergence. The development of proximal, tonic, and accommodative vergence will be discussed in this section, followed by discussion of the ability to correct for the remaining alignment error using disparity-driven vergence.

A pure proximity cue can elicit a vergence response in adults^{155–157} (see Ref. 158 for review). This is important, as it has been shown that reflex vergence responses to disparities larger than 5° are less robust than those to smaller stimuli, even in adults.^{158–160} A proximal cue may therefore provide an important stimulus to initiate a large change in vergence. As discussed earlier, while it does not appear that infants respond to some pictorial cues (familiar size, linear perspective) until around 4 to 6 months of age, it does appear that they are sensitive to looming information as early as 3 to 4 weeks of age.^{109–111} Thus there is the potential for infants to use proximity cues to drive vergence responses from the first weeks after birth.

The tonic resting position of the vergence system describes the underlying alignment of the eyes in the absence of all other components of the vergence response. For high hyperopes, a relatively *divergent* baseline tonic position might be advantageous as it could compensate for increased accommodative

convergence and avoid a convergent misalignment. Aslin¹⁶¹ found the mean vergence position in the dark in infants to be more convergent than in adults; 1- to 4-month-olds had a dark vergence position of approximately 25 cm, 6- to 18-month-olds were aligned at 50 cm, and adults at 100 cm. This convergent behavior would appear to put the youngest infants at risk for overconvergence with the addition of accommodative convergence, although the accommodative posture in the dark was unknown in this particular study, so the contribution of accommodative convergence to the measurements was unknown. As the head grows and the extraocular muscles mature, the vergence system must also compensate for developmental changes to avoid errors in alignment. Evidence of short-term adaptive realignment has been exhibited in typical adults who are given a manipulated vergence demand.^{133–136} This adaptation has been attributed to the tonic component of the response^{60,134,162} and, if present in development, could play a role in compensation for changes in demand with growth. Thus far it has been determined that 5- to 12-year-old children have more adaptable tonic vergence responses than adults,¹⁶³ but adaptation of tonic vergence in younger children and infants has not been studied.

In the clinic, the gain of the coupling from accommodation to vergence is typically quantified using the ratio of accommodative convergence to accommodation (AC/A, in angular units per diopter, pd/D). Aslin and Jackson¹⁶⁴ were the first to demonstrate a vergence-type eye movement under monocular viewing (disparity open-loop conditions) and therefore the likely presence of accommodative vergence in 2- to 6-month-olds, although a proximal cue was also present. They did not have equipment to measure accommodative responses, however, and were not able to quantify the AC/A relationship. Turner et al.¹⁴⁰ were able to measure the AC/A ratio for real moving stimuli viewed monocularly in 1-week- to 1-year-old infants, 3-year-olds, and adults. They noted that there was a statistically insignificant change in the ratio with age in meter angles per diopter (MA/D), although the variance in the estimates was large: The mean value from birth to 8 weeks of age was 0.93 MA/D (SD ± 1.0) and in adults was 0.75 MA/D (SD ± 0.7). A similar result was obtained by Bharadwaj and Candy,⁷⁰ who noted the average AC/A ratio in MA/D to be between 0.7 and 0.8, irrespective of age, from the first months after birth to 46 years of age. These estimates in MA are in units related to viewing distance, whereas the change in IPD with age implies that the angular rotation of the eyes would change in degrees or prism diopters across this age range. For example, taking IPDs from MacLachlan and Howland¹⁶⁵ and applying them to the AC/A ratios from Turner et al.,¹⁴⁰ 0.93 MA/D multiplied by 4.3 cm gives an infant AC/A ratio of 4.0 pd/D at 8 weeks of age, and 0.75 MA/D multiplied by 6.1 cm gives an adult AC/A ratio of 4.6 pd/D. While, as just shown, a larger calculated ratio in one unit does not mean a larger calculated ratio in the other unit, the significance of the differences in a practical sense remains to be determined. It should also be noted that the ratio of measured responses is particularly informative in comparison with typical clinical approaches that record only the numerator of the ratio and assume that the response in the denominator is accurate for the stimulus. In the case of the AC/A ratio, the accommodative system typically exhibits a reduced gain, or increasing lag; so a ratio based on the comparison of the actual responses reveals more vergence per diopter of accommodation compared to estimates with the stimulus rather than the response in the denominator.

The components listed above provide an infant or young child with a vergence response that is not driven by a disparity cue. In some weighted combination,^{166–168} they would result in a vergence position that may or may not equal the demand.

In models of vergence responses,^{59,60,153,154,169} any remaining error is then corrected by feedback provided by disparity-driven or fusional vergence, and an individual will presumably not become strabismic if his or her motor fusional vergence range is large enough to overcome the error.

Retinal disparity is defined as the relative angular displacement of corresponding images in the two eyes when viewing an object binocularly. It can be defined as an absolute angular displacement from the fixation point, termed absolute disparity, or as the relative angular displacement between two points or objects in a scene independent of the fixation location, termed relative disparity (see Ref. 170 for review). Evidence of realignment eye movements to changes in absolute disparity in early infancy has been provided in studies in which a prism was placed in front of one eye.^{142,145} While infants do not appear to respond to small prism displacements (5 and 10 pd base-out, approximately 3° and 6°, respectively) until 6 months of age,¹⁴² 50% of the 2-month-old and 100% of the 4-month-old infants displayed a refixation response to a large prism displacement (20 pd base-out, approximately 11°).¹⁴⁵

The visual information used to drive these early realignment responses to disparity is unclear (see Refs. 143, 171, 172). Adults can typically detect relative disparities as small as 0.2 to 2.0 minutes of arc.^{173–175} The first studies measuring relative disparity sensitivity in human infants found onset to occur rapidly between approximately 3 and 5 months of age, to disparities of between 1° and 1 minute of arc.^{174,176–179} These studies used either behavioral or VEP methodology, and found that most infants could achieve a stereoacuity of 1 minute of arc by 20 weeks of age.^{174,179} These datasets might suggest that infants are not sensitive to disparity prior to 3 to 5 months of age; however, recent adult studies suggest that absolute disparity can be processed in the first stages of cortical processing prior to the availability of relative disparity responses.^{170,180–182} Therefore, absolute disparity could feasibly be available earlier in postnatal development than relative disparity cues. Neural control of vergence eye movements also involves both subcortical and cortical activity in adults, with the latter developing more slowly after birth (see Ref. 183 for review). Neurons in V1,^{180–182,184} the medial superior temporal (MST) area,¹⁸⁵ and the frontal eye fields (FEF)¹⁸⁶ have been shown to display sensitivity to disparity information related to vergence eye movements. Furthermore, areas MST¹⁸⁵ and FEF¹⁸⁶ have also demonstrated activity corresponding to the dynamics of the vergence motor response. The development of vergence responses may therefore be limited by the maturation of these cortical areas. Neurons in area V1 show sensitivity to coarse disparity as early as 6 days of postnatal age in infant monkeys,^{149,187} which, on the loose ratio of 1:4,¹⁸⁸ would suggest by approximately 1 month in humans. Less is known about the time course of development of MST and FEF in relation to vergence eye movements. As these areas come online during development, however, we might expect to see improved control of dynamic vergence tracking responses (via input from MST) and of voluntary responses (via input from FEF). In summary, while preferential looking and VEP responses to relative disparity emerge at 3 to 5 months of age in humans, it is feasible that vergence responses could be driven by disparity at earlier ages. In fact, Brown et al.¹⁷¹ have suggested that the preferential looking and VEP relative disparity responses in the youngest human infants may be limited by contrast processing rather than disparity processing per se.

A second proposal to explain how infants might achieve motor alignment before exhibiting sensitivity to relative disparity has been that the two eyes fixate the target independently in the first months after birth before the responses to relative disparity develop.^{68,189,190} Aligning each

eye independently in the same time frame would be consistent with the outward appearance of a coordinated vergence response. The earlier development of subcortical mechanisms, the superior colliculus, for example,¹⁹¹ compared to visual cortical areas could permit early independent fixation with the two eyes, before cortical sensitivity to disparity becomes an informative cue.¹⁹² Aslin¹⁹⁰ argues against such a theory using indirect evidence, however, noting that (1) newborn infants can realign their eyes to complex targets at multiple distances,¹³⁹ evidence of some ability to identify corresponding points; and (2) young infants display accommodative convergence responses, with accommodative effort also matched in the two eyes,^{140,164} demonstrating that vergence motor responses are present but not whether they can be driven by disparity. The role of this independent bifoveal fixation hypothesis in the first months after birth is difficult to test directly and to distinguish from a disparity-driven response, in that any situation in which the eyes are both given an object to fixate will also provide disparity information. Clearly, however, infants breaking down into all forms of strabismus are unable to use bifoveal fixation to maintain alignment. Therefore, if it is present, bifoveal fixation is not a robust mechanism even at the early ages at which infantile esotropia develops,^{193–195} when either eye alone is still able to take up fixation in monocular conditions even in the presence of the deviation.

To summarize, the average onset of refractive esotropia at 2 to 3 years of age cannot be attributed to typical vergence development, as responses become largely adult-like by 3 to 5 months of age. Nonetheless, it still remains to be understood how the different components of the vergence response—that is, proximity, accommodative convergence, tonic, and disparity-driven responses—might interact to drive vergence in infancy and early childhood. Their balance is particularly important in high hyperopes, as a large accommodative demand has the potential to drive an overconvergence and lead to refractive esotropia. The likelihood that a child will decompensate into a strabismus would also depend on the motor fusional vergence range available to overcome vergence error resulting from the combination of the other components.

The Development of Refractive Esotropia

When one is comparing absolute demands, it is the youngest infants who are likely to have the largest apparent conflict between their accommodative and vergence demands and therefore may experience the most stress on their visual system as a result of the neural coupling (Fig. 3). As discussed above, spherical equivalent refractive error at birth is more hyperopic than found in adults.^{35,196} In contrast, infants have a reduced IPD relative to adults^{165,197}; those under 1 year of age have a mean IPD of 43 mm (SD ± 3 mm); 3-year-old children have a mean of 49 mm (SD ± 2.6 mm); and adults have a mean of 61 mm (SD ± 3.2 mm).¹⁶⁵ Thus, in the simplest sense, a larger accommodative response is required to eliminate defocus while a smaller angular vergence response is required to align the eyes during infancy. These demands change over the course of development as a result of emmetropization and growth of the head.

The impact of physiological and mechanical immaturities of the eye on the neural innervation to accommodation and vergence is currently unclear. For example, the lens is more pliable in youth than in adulthood,^{198,199} implying that the innervation to accommodation and accommodative convergence could actually be reduced. However, the eye is also around 70% of the adult size^{200,201} and therefore presumably has less inertia during a vergence movement. Hence the neural innervation or effort required to achieve accurate accommo-

dation in infancy is unknown, and therefore the effort driving accommodative convergence is also unknown. Nonetheless, newborns, with the levels of hyperopia associated with refractive esotropia in older children, routinely maintain eye alignment. If they are going to develop refractive esotropia, they do not do so for months or years after birth.

What might protect hyperopic infants from the strabismus? If, as suggested by the classical explanation for refractive strabismus, the strabismus results from excessive accommodative convergence, candidate protective mechanisms might include reduced accommodative activity, a low AC/A ratio, large fusional vergence ranges, or an increase in any component of the accommodative response that does not drive accommodative convergence during infancy. For example, in adults, tonic accommodation does not drive accommodative convergence, and its adaptation has been shown to play a role in maintaining binocular motor behavior^{57,126,202} (but see Ref. 59). If this were also the case during infancy, increased tonic accommodation would help reduce the impact of hyperopia on the vergence response. A high CA/C ratio would also drive accommodation and help overcome the hyperopia without driving additional accommodative convergence. Overall, even a simple change in the relative weighting of these components in the final combined motor response could relieve stress on the vergence system and potentially protect a hyperopic infant from the strabismus.

Is there evidence that any of these candidates are relieving stress on the vergence system? Most components have not been studied in this context to date, but currently the literature does suggest, as discussed above, that the youngest infants may have both a reduced AC/A ratio in pd/D^{52,70,140} and an increased CA/C ratio relative to adults.¹³⁸ More data are required to confirm this hypothesis in individuals, however. As these ratios mature and potentially become less protective, they might provide one explanation for the later onset of the strabismus. The processes underlying any maturation in the response ratios are unknown. An estimate of the AC/A or CA/C ratio is merely the ratio of the motor responses, with one system in open-loop viewing conditions for its primary cue. The ratio could mature as a result of any factor that changes one motor response relative to the other, including maturation of the mechanical plant (the mechanical properties of the lens, e.g.) or innervation at any relevant stage of the neural circuitry.

There has been anecdotal speculation that infants simply do not need to accommodate very much until the second year after birth, based on their typical activities, and therefore their accommodative convergence is not excessive until that time. While infants do progress to more sustained attention over the first year after birth,⁸⁸⁻⁹¹ they are still fixating on objects at short viewing distances from the first months after birth as they start to reach and grasp.⁸⁵⁻⁸⁷ The literature also shows that typical infants have highly active accommodation and vergence systems at least after 3 months of age.^{64-69,76,77,140-143,146} In contemplating this hypothesis as the sole explanation for the delay in onset of strabismus, one might therefore ask why these infants, who have apparently been aligned in early development, switch to tolerating misalignment and potentially diplopia at an age when they are still essentially free to select their activities, with no school or environment where they have defined tasks to perform. These patients also decompensate into the strabismus at ages from approximately 6 months to 6 years, a range over which their daily activities are very different. Although it is feasible, it appears that typical daily activities are unlikely to be the sole key explanation for the onset of the strabismus. Understanding the triggers that precipitate the change in behavior and strabismus over such a wide age range will be central to defining the patients with the most

risk. Does an earlier onset, at 6 months, indicate a greater severity of a critical factor than an onset at 5 years (e.g., see Ref. 203)? Even patients who have had infantile esotropia and then go on to develop refractive esotropia after surgical alignment exhibit a typical age of onset of refractive esotropia,^{152,204} suggesting that the precipitating factors may be consistent even in these patients with disrupted early visual experience.

Why do only some hyperopes develop the strabismus, and even with a prescribed optical correction? As infants age, some will emmetropize and no longer be at risk for strabismus^{31,36,38}; some will retain their hyperopia but not develop strabismus; and approximately 20% with hyperopia above +3.5 D will develop strabismus.⁹⁻¹¹ Why might only the latter subset decompensate after maintaining alignment during the early postnatal period, even with compliant use of preventive spectacle correction in some cases (Fig. 29-11)? Family history,^{37,43-49} anisometropia,^{37,50} and sensory binocular function^{1,3,37,150,151} have all been implicated, but what can we learn from oculomotor performance?

The AC/A ratio has certainly been implicated; there are patients with accommodative esotropia and low hyperopia whose deviation is attributed to a high AC/A ratio alone (e.g., Ref. 19). It has been suggested that individuals with refractive strabismus have higher AC/A ratios than those hyperopes who do not develop esotropia.^{52,205,206}

Although typical infants are accommodating relatively accurately from approximately 3 months of age, a number of studies have also suggested that there are individual differences across subjects as some higher hyperopes demonstrate an increased accommodative lag into childhood.^{71,72,207,208} If this is an active strategy, it would suggest that these infants might be favoring single vision over clear vision by tolerating increased lag and blur to avoid overconvergence and diplopia. Do all infants and young children demonstrate a reliable bias toward seeing singly (accurate vergence) or clearly (accurate accommodation)? Bharadwaj and Candy⁵⁸ demonstrated that, in the presence of 2 D or MA step stimuli (the introduction of -2 D lenses or 2 MA base-out prisms), typically developing subjects from 2 months to 12 years of age tended to produce equal numbers of responses to each and therefore, on average, did not exhibit a significant bias at this level of induced conflict between accommodation and vergence. It remains to be seen if some, possibly higher, hyperopes do maintain a bias, particularly if their accommodative and vergence systems are under stress. An individual demonstrating a bias to seeing singly might tolerate a lag of accommodation and be protected from strabismus, while an individual demonstrating an extreme bias to seeing clearly might be at high risk for strabismus due to an increased accommodative response (driving accommodative convergence).

When looking at the higher hyperopes who exhibited large lags, Ingram et al.^{207,209} found that the individuals with refractive strabismus tended to have a lag of accommodation prior to the onset of the deviation while those who accommodated more accurately tended to not develop strabismus. This is inconsistent with the hypothesis from the previous paragraph, which suggested that it is the high hyperopes who accommodate accurately who would be at the most risk for overconvergence. If the development of the strabismus is indeed related to the neural coupling of accommodation and vergence, the data of Ingram et al.²⁰⁷ suggest that (a) the children who are underaccommodating prior to the onset of strabismus are actually unable to compensate for the conflict relative to their peers, and (b) those who are accommodating well are maintaining accurate responses for their age in both systems. If this hypothesis is correct, that large accommodative lags indicate a strategy to avoid diplopia from excessive accommodative convergence, at

some point the individuals at risk are no longer able to sustain the strategy, and a strabismus becomes somehow unavoidable or tolerable in some sense. The age at which this occurs appears to vary as discussed above.¹⁹

In parallel, Ingram et al.²⁰⁷ and Mutti et al.³⁸ have indicated that the individuals with the larger accommodative lags are also the ones who are less likely to emmetropize. These data are inconsistent with the consensus from the animal models demonstrating that unilateral or bilateral defocus leads to adjusted growth of the eye and emmetropization.^{39–42,210} Instead they suggest that bilateral hyperopes experiencing increased hyperopic retinal defocus are actually less likely to emmetropize than their peers, who accommodate more accurately. Given the association between increased hyperopia and refractive strabismus, poor emmetropization indirectly increases the infant's risk for strabismus, at least statistically. There is also a literature suggesting that some refractive esotropes experience an increase in their hyperopia after the onset of the strabismus.^{211–216}

The individuals who develop esotropia despite having their hyperopia optically corrected are particularly interesting in the context of the classical explanation for refractive strabismus^{9–11} (Fig. 2). In theory, the optical correction should reduce or normalize the patient's accommodative demand, yet these patients are reported to decompensate into esotropia at ages similar to those of the uncorrected hyperopes. Relatively simple candidate explanations for this outcome include poor compliance with the spectacle correction (although this was explored somewhat in these studies) plus family history. Why might these individuals decompensate when a standard treatment for classical uncorrected early refractive esotropia is to provide the hyperopic spectacle correction and expect realignment with reduction of the accommodative demand?^{56,217,218} Is there some form of motor adaptation once glasses are provided to a nonstrabismic infant that might place the individual at risk again even though he or she is wearing preventive correction? It is also not uncommon for patients with refractive esotropia to become realigned when they are first given glasses but deviate again at a later age.^{219–221} Does their family history destine them to develop strabismus irrespective of the correction? Would they have realigned with glasses after the onset of strabismus if the glasses had not been prescribed beforehand? This is a highly complex topic, but may lead to significant insights if the development of strabismus after optical correction can be studied in a systematic fashion.

From this theoretical perspective, it is informative to reconsider how some hyperopic infants might escape strabismus while others develop a refractive esotropia. As discussed in the preceding sections, a typical hyperopic infant needs to generate increased accommodation responses, when compared to an adult, and reduced angular rotation in vergence responses to remain both focused and aligned. This would be relatively simple if the two systems were independent and not coupled. The presence of the coupling complicates this goal as a patient without a strabismus must either (1) limit the convergence driven by the accommodation by having a low response AC/A ratio^{52,205} or by generating accommodation responses via pathways that do not drive the coupling, using tonic accommodation or convergence accommodation, for example; or (2) reduce the impact of accommodative convergence innervation by having a divergent tonic vergence position, limited proximal vergence, or adequate divergent fusional ranges²⁰⁵; or (3) tolerate large accommodative lags to prevent overconvergence driven by the coupling. This third scenario is proposed to underlie the development of bilateral isometric amblyopia and may also be a strategy adopted by some individuals prior to the development of a refractive

esotropia, as noted by Ingram et al.²⁰⁷ The factor or factors that cause a patient to then decompensate into strabismus at some time in infancy or early childhood are yet to be definitively determined and appear more subtle than the simplest classical hypothesis of high levels of hyperopia. Their nature and our ability to manipulate them have key implications for the success of preventive vision screening. Ingram et al.¹⁰ and Atkinson et al.^{9,11} agreed that the prevalence of severe amblyopia was reduced by preventive optical correction, but the data regarding the prevention of refractive esotropia are less clear and potentially less promising.

How might the analysis above inform current approaches to the screening and management of young hyperopes? The different theoretical clinical approaches are laid out in a flowchart in Figure 4. This figure includes both vision screening and comprehensive eye examinations and, as demonstrated by the pathway illustrated in black, the only approach that leads to an active prevention of strabismus is the ultimate provision of glasses to an aligned hyperope who would have developed strabismus in the absence of the optical correction. There are a number of paths by which the patient can receive a full examination, but the one illustrated in black is the only one that is a systematic path without an opportunistic referral. This flowchart does not address the issues of the ages at which infants and children should be screened or examined, or the criteria that should be used for failing a screening or for prescribing glasses, or whether full or partial correction should be prescribed, or the benefits of prescribing hyperopic correction to a child who is not at risk for strabismus. It does, however, help put the questions considered above into context. Firstly, the Atkinson and Ingram studies^{9–11} suggest that only approximately 20% of higher hyperopes will develop strabismus (Fig. 1), implying that the specificity of a management approach for preventing strabismus based solely on refractive error would be quite poor. Other factors, such as family history or perhaps the oculomotor characteristics discussed above (e.g., adaptation or coupling ratios) form logical additional candidates worthy of consideration. Secondly, if the classical explanation for the strabismus, excessive accommodative convergence, is indeed the primary factor, prescribing enough hyperopic correction at the right age should prevent the strabismus. Current evidence, however, suggests that an apparently significant proportion of patients will develop the strabismus even with correction (Fig. 2). This complex problem, in turn, warrants clarification and scrutiny as, in the simplest sense, it challenges the underlying classical explanation for the strabismus. In contrast, numerous strabismic patients do appear to realign when glasses are prescribed rapidly after the onset of the strabismus. How can these sets of data be reconciled? Lastly, the data of both Ingram et al.¹⁰ and Atkinson et al.^{9,11} suggest that the prevalence and severity of amblyopia at the end of their studies were improved with optical correction and therefore the impact of correction for hyperopia, beyond its role in strabismus, must also be borne in mind.

Overall, this analysis appears timely in that prescribing guidelines for hyperopia are still largely consensus based (e.g., Ref. 222), yet there is increasing pressure to undertake screening at earlier ages. The goal of this review was to evaluate additional aspects of oculomotor accommodation and vergence performance that might prove to be informative in the decision to prescribe, for those who would like to attempt prevention rather than treatment of this form of strabismus.

CONCLUSIONS

It is apparent from the literature reviewed here that infants typically have active accommodation and vergence responses

FIGURE 4. Clinical approaches to diagnosis and management of refractive esotropia. Both vision screening and comprehensive eye examination are included. The pathway illustrated in *black* is the only pathway leading to active prevention of strabismus that is a systematic path without an opportunistic referral.

by 3 to 6 months of age. At this stage of development, a number of response components or cue combinations are feasibly being used. How these components of oculomotor responses combine to prevent or precipitate refractive strabismus in apparently matched individuals is poorly understood yet potentially key in efforts to prevent vision loss. While factors such as family history are clearly significant, if we are to make progress in preventing rather than treating developmental forms of esotropia attributed to accommodative effort, it appears that we must make progress in understanding (a) how individuals manage their combined accommodation and vergence motor responses given the response components available to them, and (b) how so many individuals are apparently able to avoid an esotropia, even in the presence of hyperopia, anisometropia, and significant family history. It is hoped that this understanding could be provided to clinician scientists undertaking large-scale prospective studies of preventive strategies.

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