**Refractive Development: Main Parts**

- Prevalence of refractive errors and changes with age.
- Factors affecting refractive development.
- Operational properties of the vision-dependent mechanisms that mediate emmetropization.
- How visual signals are transformed into biochemical signals for eye growth.

**Distribution of Refractive Errors**

(Young adult population)

- Major differences from random distribution:
  - More emmetropes than predicted
  - Fewer moderate errors (e.g., -2.0 D)
  - More high errors (e.g., -6.0 D)

- Leptokurtotic distribution

**Changes in Refractive Error with Age**

- Age norms of refraction (Slataper, 1950)
- Average data are not very predictive of changes on an individual basis before about 20 years. Thereafter, most people experience the same trends.

**Myopia in Premature Infants**

- Myopia associated with short axial lengths & steep corneas.
- Recovery primarily due to corneal flattening.

**Human Infants**

- Emmetropization is the process that guides ocular growth toward the optimal optical state. It occurs very rapidly; most infants develop the ideal refractive error by 12-18 months.
During the period of rapid emmetropization, the degree of anisometropia typically decreases (i.e., "isometropization" occurs).

**Axial Length Development**

- **Rapid Infantile phase**: 0-3 yrs — axial length increases about 5-6 mm.
- **Slower Juvenile phase**: 3-14 yrs — axial length increases about 1 mm.

**Corneal Development**

- Major Optical Changes:
  1) flatter cornea (6-8 D)
  2) deeper AC (0.8 D)
  3) flatter lens (12-15 D)

**Anterior Chamber Depth**

- AC depth increases from about 2.4 mm at birth to about 3.5 mm at 3 years (about 0.8 D).

**Lens Development**

- Major Optical Changes:
  1) flatter cornea (6-8 D)
  2) deeper AC (0.8 D)
  3) flatter lens (12-15 D)
Changes with Age

From about 2 to 7-8 years, the mean refractive error is quite stable & the degree of variability is low.

During early adolescence, the cornea is relatively stable. The slow decrease in lens power is counterbalanced by an increase in axial length.

Refractive Development: Early School Years

Anterior Chamber Depth

Refractive Development: Early School Years

Lens Thickness

Refractive Development: Early School Years

Anterior Segment

Prevalence of Myopia in Humans

The decrease in mean refractive error between about 8 and 20 years is due primarily to the onset of “school” myopia in a small proportion of the population.
**Myopic Progression**

"Youth-Onset" or "Juvenile-Onset", or "School" Myopia

For many individuals, myopic progression stops in late teenage years...associated with the normal cessation of axial growth.

**Age of Onset vs. Degree of Myopia**

The earlier the onset of myopia...the higher the rate of progression and the final degree of myopia.

**Axial Nature of Myopia**

The rate of myopic progression is highly correlated with the rate of axial elongation.

**Predictability of Refractive Errors at Age 13-14 Years**

Refractive Error Distributions for Children at 5-6 years who develop:
- Myopia >0.50 D
- Emmetropia -0.49 to +0.99 D
- Hyperopia >1.0 D

**Classifications of Myopia**

- Congenital = present at birth & persists through infancy
- Youth-onset = occurs between 6 years and early teens
- Early adult-onset = occurs between 20 & 40 years
- Late adult-onset = occurs after 40 years
McBrien & Adams, 1997

Early Adult Onset Myopia

Examples of adult onset myopia associated with a change in occupation.

Adult Progression

Change in refractive error for myopic subjects following onset of microscopy career. 48% of myopes showed myopic changes >0.37 D (i.e., myopic progression).

Median age = 29.7 years

Change in refractive error for myopic subjects following onset of microscopy career. 48% of myopes showed myopic changes >0.37 D (i.e., myopic progression).

Age Norms of Refraction

(Slataper, 1950)

Changes in Refractive Error with Age

Acquired hyperopia due to:
1) presbyopia
2) lens continues to flatten
3) refractive index of lens cortex increases

Vitreous Chamber

young adult (22 yrs) = 16.14 mm
Mature adult (54 yrs) = 15.7 mm

Ooi & Grosvenor, 1995

Decrease in hyperopia due to increase in refractive index of core of crystalline lens.

Lens Development - Mass

The crystalline lens continues to grow throughout life.

Changes in Refractive Error with Age

Age Norms of Refraction

(Slataper, 1950)

Weale, 1982

Weale, 1982

Age Norms of Refraction

(Slataper, 1950)
Astigmatism is the most common ametropia. The magnitude is, however, usually relatively small.

**Prevalence of Astigmatism**

- **Amount of Astigmatism (D)**: 0.0, 0.5, 1.0, 1.5, >2
- **Percentage of Population**: 0, 10, 20, 30, 40, 50

**Prevalence of Astigmatism: Infants**

- Marked levels of astigmatism are common in young infants – due primarily to corneal toricity.

**Prevalence of Astigmatism (>1 D)**

- **Age (weeks)**: 0, 10, 20, 30, 40, 50
- **Prevalence (%)**: 0, 20, 40, 60, 80, 100

**Longitudinal Changes in Astigmatism**

- Almost every infant shows a decrease in astigmatism during early infancy. Early astigmatism may not be very predictive of astigmatism later in life.

**Axis of Astigmatism**

- Right eye astigmatism at 9 months of age (n = 143, Cambridge, UK). W-t-R astigmatism predominates.
Change in Axis of Astigmatism

With age the prevalence of W-R decreases & there is a concomitant increase in A-R. Most of the changes occur after about 35 years of age and occur at a rate of about 0.25 D every 10 years.

Change in Corneal Power & Astigmatism

After age 35 years, the cornea gets progressively steeper. The reduction in the radius of curvature is greater for the horizontal meridian.

Distribution of Refractive Errors

(young adult population)

Major differences from random distribution:
- more emmetropes than predicted
- fewer moderate errors (e.g., -2.0 D)
- more high refractive errors (e.g., -6.0 D)

Nature of Refractive Errors

Not all emmetropic eyes are alike:
Ks = 39.0 – 47.6 D
Lens = 15.5 – 23.9 D
AC = 2.5 – 4.2 mm
AL = 22.3 – 26.0 mm
Ametropic eyes between -4 D and +6 D frequently have individual ocular components that fall within the range for emmetropic populations. With larger ametropias, one component, typically axial length, falls outside the range for emmetropia.

My Eyelash

About 200 microns

Frequency Distributions for Individual Ocular Components

Since the distribution of refractive errors is leptokurtic, there can not be free association between individual components. Highest correlation is typically found between refractive error and axial length.
Factors that influence refractive state

- Genetic Factors
  - ethnic differences in the prevalence of refractive errors
  - familial inheritance patterns
  - monozygotic twins
  - candidate genes

- Environmental Factors
  - humans: epidemiological studies of prevalence of myopia
  - lab animals: restricted environments
  - lab animals: altered retinal imagery

Ethnic Category

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Swedish</th>
<th>British</th>
<th>Israeli</th>
<th>Malay</th>
<th>Indian</th>
<th>Eurasian</th>
<th>Chinese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of Myopia (%)</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
</tr>
</tbody>
</table>

Prevalence of Myopia in Different Ethnic Groups

If both parents are myopic, the child is 4-5 times more likely to be myopic than if neither of the child’s parents are myopic.

Familial Inheritance Patterns

<table>
<thead>
<tr>
<th>Percent Children Myopic</th>
<th>None</th>
<th>One</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Monozygotic Twins

Evil twin? Good twin?

Identical twins have very similar refractive errors.

Monozygotic Twins

Concordance of Optical Components

Not only do twins have identical refractive errors, their eyes have very similar dimensions.

Concordance limits:
- Axial length = 0.5 mm
- corneal & lens power = 0.5 D
- AC depth = 0.1 mm
- lens thickness = 0.1 mm
- total power = 0.9 D
**Genetic Loci for Myopia**

**1990-2003**

<table>
<thead>
<tr>
<th>Locus</th>
<th>Location</th>
<th>Study</th>
<th>Myopia Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYP1</td>
<td>Xq28</td>
<td>Schwartz et al, 1990</td>
<td>-6.75 to -11.25 D</td>
</tr>
<tr>
<td>MYP2</td>
<td>18p11.31</td>
<td>Young et al, 1998</td>
<td>-6.00 to -21 D</td>
</tr>
<tr>
<td>MYP3</td>
<td>12q21-q23</td>
<td>Young et al, 1998</td>
<td>-6.25 to -15 D</td>
</tr>
<tr>
<td>MYP4</td>
<td>7q26</td>
<td>Naiglin et al, 2002</td>
<td>Avg = -13.05 D</td>
</tr>
<tr>
<td>MYP5</td>
<td>17q21-q22</td>
<td>Paluru et al, 2003</td>
<td>-5.50 to -50 D</td>
</tr>
</tbody>
</table>

**2005 to 2009**

<table>
<thead>
<tr>
<th>Locus</th>
<th>Location</th>
<th>Study</th>
<th>Myopia Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYP6</td>
<td>23p12</td>
<td>Stambolian et al, 2004</td>
<td>-1.08 D or lower</td>
</tr>
<tr>
<td>MYP7</td>
<td>1p13</td>
<td>Hammerton et al, 2004</td>
<td>-12.12 to -7.25 D</td>
</tr>
<tr>
<td>MYP8</td>
<td>5q26</td>
<td>Hammerton et al, 2004</td>
<td>-12.12 to -7.25 D</td>
</tr>
<tr>
<td>MYP9</td>
<td>4q12</td>
<td>Hammerton et al, 2004</td>
<td>-12.12 to -7.25 D</td>
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<tr>
<td>MYP10</td>
<td>6p23</td>
<td>Hammerton et al, 2004</td>
<td>-12.12 to -7.25 D</td>
</tr>
<tr>
<td>MYP11</td>
<td>4q23-q27</td>
<td>Zhang et al, 2006</td>
<td>-5 to -30 D</td>
</tr>
<tr>
<td>MYP12</td>
<td>2q27.1</td>
<td>Paluru et al, 2005</td>
<td>-7.25 to -27 D</td>
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<tr>
<td>MYP13</td>
<td>6p21-p26</td>
<td>Zhang et al, 2006</td>
<td>-6.00 to -10 D</td>
</tr>
<tr>
<td>MYP14</td>
<td>1p36</td>
<td>Wojnowski et al, 2006</td>
<td>Avg = -3.46 D</td>
</tr>
<tr>
<td>MYP15</td>
<td>10p11.1</td>
<td>Rollinson et al, 2007</td>
<td>Avg = -7.38 D</td>
</tr>
<tr>
<td>MYP16</td>
<td>6p15.33-p15.2</td>
<td>Lam et al, 2008</td>
<td>-7.13 to -16.88 D</td>
</tr>
<tr>
<td>MYP17</td>
<td>1q41</td>
<td>Klein et al, 2007</td>
<td>Range of Errors</td>
</tr>
<tr>
<td>MYP18</td>
<td>7p10</td>
<td>Klein et al, 2007</td>
<td>Range of Errors</td>
</tr>
<tr>
<td>MYP19</td>
<td>23q11.29-q23.2</td>
<td>Klein et al, 2007</td>
<td>Range of Errors</td>
</tr>
<tr>
<td>MYP20</td>
<td>7q15</td>
<td>Cicer et al, 2008</td>
<td>Avg = -3.47 D</td>
</tr>
<tr>
<td>MYP21</td>
<td>3p26</td>
<td>Andrew et al, 2006</td>
<td>-20 to -6.75 D</td>
</tr>
<tr>
<td>MYP22</td>
<td>22q11.23-q23.2</td>
<td>Cicer et al, 2009</td>
<td>Avg = -9.34 D</td>
</tr>
<tr>
<td>MYP23</td>
<td>6p14.11</td>
<td>Li et al, 2006</td>
<td>&lt; 5.06 D</td>
</tr>
<tr>
<td>MYP24</td>
<td>15p14</td>
<td>Schulte et al, 2006</td>
<td>Range of Errors</td>
</tr>
</tbody>
</table>

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**Myopia has historically been associated with nearwork.**

![Tschering, 1882](Duke-Elder, 1970)

**Significant Associations in Myopia**

- **Myopia & Intelligence**
  - IQ Score (80-96, 97-103, 104-111, >111)
- **Myopia & Education**
  - Years of Education (<8, 9, 10, 11, >12)

**An Epidemic of Myopia**

- Taiwanese School Children
  - Prevalence Rate (%)
  - Average Degree of Myopia (D)
  - Lin et al., 2004
  - 2000
  - 1995
  - 1986

The prevalence and average degree of myopia is increasing rapidly over time.
An Epidemic of Myopia

The prevalence of myopia is increasing too fast to reflect genetic changes; something in the environment is affecting the pattern of refractive errors.

Restricted environments promote myopia.


Chronic Image Degradation Causes Myopia
Monocularity Form-Deprived Monkeys

The potential for a clear retinal image is essential for normal refractive development.

Emmetropization Requires Vision

Normal Monkeys
Dark-reared Monkeys

Guyton et al., 1987

FDM occurs in a wide variety of animals.
FDM occurs in a wide variety of animals—including humans—which suggests that the mechanisms responsible for FDM are probably fundamental to ocular development. The potential for a clear retinal image is essential for normal emmetropization.

**Emmetropization is guided by optical defocus.**

Optically imposed refractive errors produce predictable refractive-error changes.

**Imposed Myopia:** To compensate, the eye must become more hyperopic.

**Imposed Hyperopia:** To compensate, the eye must become more myopic.

**Negative lenses cause the eye to grow faster; positive lenses reduce growth.**

**Emmetropization:** Effective Operating Range

Moderate powered treatment lenses produce predictable changes in refractive error in many species.
A. End of Treatment

Spectacle Lens Power (D)

-8 -4 0 4 8 12

Refractive Error (D)

-8 -4 0 4 8 12

B. Effective Emmetropization Range

Effective Refractive Error (D)

-8 -4 0 4 8 12

Change in Refractive Error (D)

-12 -8 -4 0 4 8

r² = 0.76

r² = 0.85

Monkeys vs Humans

Large refractive errors produce unpredictable growth – possibly these eyes have faulty emmetropization mechanisms.

Can optical defocus predictably alter refractive development in children?

-Optically Imposed Anisometropia

Subjects: n = 13
11-year-old myopic children

Treatment: Monovision CLs
- Dominant eye corrected for distance.
- Fellow eye uncorrected or corrected to maintain <2.0 D aniso.

Results: Distance corrected eye progressed 0.36 D more than the fellow eye.

Goss, 1984

Can defocus/spectacles predictably alter refractive development in children?

Adolescent Children

Infants

Why is there little evidence that spectacles alter human refractive development?

Faulty Emmetropization; Humans vs. Monkeys; Age; Compliance (temporal integration); Spatial Integration of Visual Signals

Canpectacles predictably alter refractive development in children?

Faulty Emmetropization
- Humans vs. Monkeys
- Age
- Compliance

Additions from Atkinson et al., 1996

Age Effects: Are vision dependent mechanisms only active early in life?

Onset of Juvenile Myopia

Age (human years)

Age (monkey years)
Late Onset Form Deprivation

Temporal Integration Properties of Emmetropization

Temporal Integration Properties

Effects of Brief Periods of Unrestricted Vision on Compensation for Binocular Negative Lenses

Lens Compensation for Continuous -3D Lenses

Effects of 1 hour of vision through plano lenses on compensation for −3 D lenses.
Implications for Nearwork

- Visual signals that increase axial growth and those that normally reduce axial growth are not weighed equally.
- To stimulate axial growth, a myopiagenic visual stimulus must be present almost constantly.

What visual system mechanisms are involved in transforming a visual signal into a biochemical signal for growth?

- Afferent Components: e.g., accommodation
- Efferent Components: e.g., “blur detector”

FDM does NOT require:
1) the visual signal to leave the eye
2) sympathetic or parasympathetic inputs to the eye.

The vision-dependent mechanisms that regulate refractive development are located in the eye.

Form-Deprivation Myopia

Hemi-Retinal Form Deprivation

Hemi-field Form-Deprivation in Monkeys

Hemi-Field vs Full-Field Form Deprivation

Evidence for Local Mechanisms
• The mechanisms that mediate the effects of visual experience on eye growth are located largely within the eye and act in a regionally selective manner.
• Global mechanisms (e.g., the act of accommodation) are unlikely to play a primary role in refractive development.
Neurochemical Transmission in the Parasympathetic System

Atropine produces cycloplegia by blocking the action of acetylcholine on muscarinic receptors in ciliary muscle.

Cholinergic Receptor Subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>CNS, nerves</td>
</tr>
<tr>
<td>M2</td>
<td>Heart, smooth muscle, ciliary muscle</td>
</tr>
<tr>
<td>M3</td>
<td>Smooth muscle, exocrine glands, ciliary muscle</td>
</tr>
<tr>
<td>M4</td>
<td>CNS, nerves</td>
</tr>
<tr>
<td>M5</td>
<td>CNS, ciliary muscle</td>
</tr>
</tbody>
</table>

Atropine blocks all muscarinic receptor subtypes.

Effects of Muscarinic Agents on Form-deprivation Myopia

- Blocking actions:
  - atropine - all muscarinic sites
  - 4-DAMP - smooth muscle
  - pirenzepine - neural ganglia

Retinal dopamine is involved in FDM

Outdoor activities have a strong protective effect against myopia.

Protective effects are not associated with exercise nor do they represent a “substitution effect” for near work.

High Light Levels & Experimental Myopia

High ambient light levels retard the development of form-deprivation myopia in chicks.
High light levels slow the rate of compensation for negative lenses. The effect is blocked by dopamine antagonist.

**Activity Markers in Amacrine Cells**

Glucagon amacrine cells are more abundant than dopaminergic Acs. Tested for visual regulation of several transcription factors. Conditions that stimulate axial elongation decrease ZENK synthesis (basically glucagon activity) whereas conditions that reduce axial growth up-regulate ZENK. Glucagon AC exhibit sign of defocus information.

**Choroidal Components**

- Choroidal Retinoic Acid
- Choroidal Thickness

**Choroidal Retinoic Acid Synthesis: Mediator of Eye Growth?**

Evidence in chicks: 1) the choroid can convert retinol to all-trans retinoic acid at a rapid rate. 2) Visual conditions that increase ocular growth produce a sharp decrease in retinoic acid synthesis. 3) Visual conditions that slow ocular growth produce an increase in RA synthesis. 4) application of RA to cultured sclera inhibits proteoglycan production at physiological concentrations.
**Choroidal Mechanisms**

Changes in choroid thickness move the retina toward the appropriate focal point.

From Wallman et al., 1995

**Scleral Components**

- bFGF & TGF beta (growth factors)
- For a myopic stimulus:
  - Decrease proteoglycan synthesis
  - Decrease sulfated GAGs
  - Increase gelatinolytic enzymes

From Norton, 1999

**Possible growth factors involved in FDM**

Biochemical "stop" and "go" Signals

MD and bFGF (Basic Fibroblast Growth Factor) vs. MD and TGF-beta and bFGF (Transforming Growth Factor Beta) by Rhorer and Stell, 1994

- bFGF = basic fibroblast growth factor. TGF-beta = transforming growth factor beta.
- The broad dose response curve suggests that more than one type of FGF receptor is involved.

**Scleral Changes with FDM**

Matrix metalloproteinase (MMP-2) appears to be the major gelatinolytic enzyme in the tree shrew sclera. Form deprivation increases catabolism in the sclera. Myopic defocus reduces the degree of scleral catabolism.

From Guggenheim & McBrien, 1996

**Scleral Changes with FDM (posterior thinning)**

Decorrn is the major proteoglycan in the marmoset sclera. The rate of proteoglycan synthesis is reduced in the posterior pole of FDM.

From McBrien & Gentle, 2003

Scleral thinning occurs very rapidly in response to onset of myopia development – due to a loss of tissue (i.e., not simply stretch).
Physical Changes

- Increase / decrease in scleral creep rate
- Axial vitreous chamber depth

The scleras from eyes that are undergoing myopic axial elongation exhibit higher than normal creep rates. During recovery from FDM the scleral creep rates fell below normal values. During both emmetropization and the development of refractive errors, vision-dependent alterations in the extracellular matrix may alter the mechanical properties of the fibrous sclera making it more distensible.

Why Worry About Myopia?

The prevalence of myopia is increasing too fast to reflect genetic changes; something in the environment is affecting the pattern of refractive errors.

Ocular Sequelae of Myopia

- Posterior Subcapsular Cataract
- Idiopathic Retinal Detachment
- Open-Angle Glaucoma
- Chorioretinal Degeneration

Health Concerns

- Myopia is the 7th leading cause of legal blindness in the U.S.A. (Zadnik, 2001).
- The second highest cause of blindness in India (Edwards, 1998).
- Myopic retinal degeneration is the second highest cause of low vision in asians (Yap et al., 1990).

The idea that something about near work causes myopia has dominated thinking for centuries.
Traditional Treatment Methods

- Vision Therapy, biofeedback training
- Bifocals; distance over & under correction
- Base-in prisms
- Pharmaceutical agents:
  - cycloplegia
  - intraocular pressure

Timolol Treatment for Myopia

Timolol was effective in lowering IOP. However there was not a significant effect on the rate of myopic progression.

Control

Timolol

Timolol and Form-Deprivation Myopia

Timolol was effective in lowering IOP in young chicks (between 18 & 27%). However there was not a significant effect on the rate of myopic progression for either form deprivation or negative lenses.

Atropine Treatment for Myopia

Atropine Therapy

- Short-term side-effects:
  - photophobia & blurred vision
  - cycloplegia (need for reading glasses)
  - potential light damage to retina
  - potential elevations in IOP
  - potential systematic reactions

Atropine in the Treatment of Myopia Study

"The Atom Study"

Randomized, double-masked study of 6- to 12-year-old myopic children. Monocular 1% topical atropine vs. placebo
Chronic atropine can produce permanent alterations in the neuropharmacology of intraocular muscles and pupil size (amplitude of accommodation, acc-convergence interactions).

Adult cat treated with 1% atropine in both eyes from 4 weeks to 4 months of age.

**Key Issues**

*Are the effects permanent?*

*Is there a rebound phenomenon?*

**Pirenzepine Trials**

- Safety and efficacy of 2% PRZ ophthalmic gel in myopic children: Years 1 & 2 (Siatkowski et al., 2003 & 2004, ARVO)

- **US Phase II Trial.**
  - 8- to 12-year old children (n=174); mean age = 9.9 yrs
  - -0.75 to -4.00 D myopia; mean = -2.04 ± 0.9 D
  - Treated with 2% PRZ or placebo BID for 2 years

**Pirenzepine: Efficacy for Pediatric Myopia**

*Year-One Results*

**U.S. Study**

- N = 174
- Myopic Progression (D/year)

**Asia Study**

- N = 203
- Myopic Progression (D/year)

**Year-Two Results**

**U.S. Study**

- Proportion ≥ 0.75 D
  - PIR = 37%
  - PLC = 68%

**Dropouts**

- 12% of PIR subjects
- 0% of PLC group

**Common adverse events**

- Eyelid gel residue, blurred near vision, and asymptomatic conjunctival reactions.
Pirenzepine Trials

- Other Questions:
  - What are the mechanisms and sites of action of PRZ? (Optimal drug & deliver system?)
  - How do you identify patients who will benefit?
  - How long do you need to treat the patient?
  - Are the effects permanent?
  - Are partial effects acceptable?
  - Is it safe during pregnancy?
  - Are there long-term side effects?

New Hopes for Optical Interventions
Emmetropization: Basic Operating Properties

Central vs. Peripheral Vision

1. Visual signals from the fovea are not essential for:
   - Emmetropization
   - Form deprivation myopia
   - Recovery from induced refractive errors
   - Lens compensation

Traditional Optical Treatment Strategies for Myopia Progression

Percentage Change in Progression (%)
-30  -20  -10   0   10   20   30   40

BFs / PALs
Decrease Increase

Under-Correction
Designed to decrease the level of accommodation during near work and/or to influence the quality of foveal vision (e.g., to reduce hyperopic defocus associated with a lag of accommodation).

Central vs. Peripheral Vision

Experimental Manipulations
Monocular Foveal Ablation &
1) unrestricted vision
2) form deprivation
3) recovery from induced errors
4) hyperopic defocus (neg. lenses)

Are visual signals from the fovea essential for vision-dependent growth?
An intact fovea is not essential for normal emmetropization.

Foveal ablation does not alter the time course, efficiency or target refractive error of emmetropization, i.e., foveal signals are not essential for normal refractive development.

An intact fovea is not essential for Form Deprivation Myopia.

An intact fovea is not essential for the recovery from induced hyperopia.

An intact fovea is not essential for the recovery from induced myopia.

Central vs. Peripheral Vision

2. When conflicting signals exist between the central and peripheral retina, peripheral visual signals can dominate central refractive development.

- Peripheral form deprivation
- Peripheral hyperopic defocus
Peripheral myopic defocus can produce central axial hyperopia in chickens.

Peripheral myopic defocus has a very strong effect on central refractive error development.

Impact of peripheral vision

In monkeys...
- Peripheral form deprivation and peripheral hyperopic defocus can produce axial myopia at the fovea, even in the presence of unrestricted central vision.
- Photoablation of the fovea does not:
  - interfere with normal emmetropization.
  - prevent recovery from induced refractive errors.
  - prevent form-deprivation myopia.
  - compensation to imposed hyperopic defocus

Peripheral vision can have a substantial influence on foveal refractive development in primates.

Central vs. Peripheral Refractive Error

Refractive error varies with eccentricity. The visual signal for eye growth varies with eccentricity.

Myopes typically exhibit relative hyperopia in the periphery, whereas hyperopes show relative myopia in the periphery.
Central vs. Peripheral Vision

Adapted from Wallman, 2004

Oblate (hyperopic)

Prolate (myopic)

Spherical (emmetropic)

Shift in Central Rx vs. Peripheral Rx

Myopic Changes

Young adults with peripheral hyperopia are more likely to exhibit myopic Rx shifts during pilot training.

Pattern of Peripheral Refractive Error

Percentage of Sample

0

20

40

60

80

100

peripheral hyperopia

peripheral myopia

Percentage of Sample

0

20

40

60

80

100

peripheral hyperopia

peripheral myopia

Pattern of Peripheral Refractive Error

Peripheral Hyperopia Precedes Myopia in Children

Children who became myopic showed more peripheral hyperopia 2 years before the onset of myopia.

Relative to Onset (years)

Spatial summation favors the periphery.

The total number of neurons is much higher in the periphery.

Should we correct peripheral refractive errors?

As a consequence of eye shape and/or aspheric optical surfaces, myopic eyes may experience significant defocus across the visual field, regardless of the refractive state at the fovea.

Traditional Spectacle Lenses Increase Peripheral Hyperopia

Uncorrected Myope “Corrected” Myope

Myopic Adults

Myopic Children

Tabernero & Schaeffel, 2003

Lin et al., 2010
**Possible Implementation Strategies**

- Contact lenses
- Spectacle lenses
- Orthokeratology
- Corneal refractive surgery

Peripheral treatment strategies can provide optimal distance correction at the fovea and provide an anti-myopia growth signal in the periphery.

**Peripheral Treatment Strategies**

**MYOVISION – SPECTACLE PROGRAM**
(Sankaridurg et al., 2010)

- Chinese children 6-12 years of age
- Three treatment lens designs vs traditional SV spectacles

**Peripheral Treatment Strategies**

**Anti-Myopia Contact Lenses**
(Holden et al., 2010)

- Chinese children 7-14 years of age
- Rotationally symmetric CL vs traditional SV spectacles

**Central vs. Peripheral Treatment Strategies**

<table>
<thead>
<tr>
<th>Percentage Change in Progression (%)</th>
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<tbody>
<tr>
<td>-60</td>
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<tr>
<td>-1.2</td>
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**Anti-Myopia Spectacles**

12-month results

Children 6-12 years-old with 1 or 2 myopic parents

(-0.97 0.48D vs -0.68 0.48D, p = 0.03)

**Anti-Myopia Contact Lenses**

6- and 12-month results
all children 7 to 14 years of age

- 34% reduction in myopia (p < 0.05)
- 33% reduction in axial length

(0.41 ± 0.21 mm, n = 45 vs 0.21 ± 0.16 mm, n = 40)
**Anti-Myopia Contact Lenses**

*Children with Parental Myopia (60% of sample)*

- 49% reduction in myopia \((p=0.03)\)
- 49% reduction in axial length \((0.41 \pm 0.21 \text{mm} \text{ vs } 0.21 \pm 0.16 \text{mm})\)

**Executive Bifocals**

*(Cheng et al., 2010)*

- Progressing myopic, Chinese children \((8-13 \text{ years}, n = 135)\)
- Exec BFs with or without \(6 \Delta \) BI prism vs. traditional SV spectacles

- 55% reduction in myopia \((p=0.001)\)
- 35% reduction in axial length \((0.40 \pm 0.04 \text{ mm} \text{ vs } 0.62 \pm 0.04 \text{ mm}, p < 0.001)\)

**Simultaneous Bifocal CLs**

*(Phillips & Anstice et al., 2010)*

- Children \((11-14 \text{ years}, n = 40)\)
- Concentric multifocal \((+2.00 \text{ D Add})\) vs. SV CL in a monocular cross-over design

- Treatment Duration = 8 months

**Peripheral Treatment Strategies**

**Overnight Orthokeratology**

*(Cho et al., 2005 & Walline et al., 2009)*

- Difference After 14 Days Treatment
- \(T = \text{ Trocket} \), \(N = \text{ Norm}\)
Relative Ametropia (D)

Refractive Errors Changes with Ortho-K

from Clark et al., 2008

Ortho-K children (mean age = 9.6 yrs, n = 35) vs SV spectacles. CRAYON study reported similar results (i.e., about 50% reduction over two years).

Ongoing Ortho-K Studies: ROMIO (Cheung & Cho), MCOS (Santodomingo et al), Japan (Kakita et al), Sydney (Swarbrick et al.)

Key Practical Points

Peripheral treatment strategies:
- should be initiated as early as practical.
  - It is likely that optical treatment strategies only slow progression.
  - Should not be limited to children
- will be of greatest benefit for individuals destined to develop high degrees of myopia.
  - Need to develop better methods to identify fast progressors.
- will probably be most effective when implemented via contact lenses.
  - More aggressive treatment zones than SV spectacles.

Key Issues

Do the treatment effects “saturate”? e.g., COMET study

Myopic Progression

Gwiazda et al., 2003

Key Issues

- Is it possible to prevent the onset of myopia?

Nature of Refractive Errors

Not all emmetropic eyes are alike.
- Ks = 39.0 – 47.6 D
- Lens = 15.5 – 23.9 D
- AC = 2.5 – 4.2 mm
- AL = 22.3 – 26.0 mm

Ametropic eyes between -4 D and +6 D frequently have individual ocular components that fall within the range for emmetropic populations. With larger ametropias, one component, typically axial length, falls outside the range for emmetropia.