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

Efferent Components
- e.g., accommodation

Afferent Components
- e.g., “blur detector”

FDM used as a tool to determine what components are important.
FDM in primates

FDM does NOT require:
- the visual signal to leave the eye
- sympathetic or parasympathetic inputs to the eye.
Restricted Form Deprivation

Selectively depriving a portion of the eye restricts the axial elongation and myopia to the deprived areas.

Wallman et al. 1978
The mechanisms that mediate the effects of visual experience on eye growth are located largely within the eye. Activity at a given retinal location controls the growth of the adjacent sclera.
**Key points:** 1. Ocular growth regulated by retinal responses to optical image. 2. Accommodation, by its influence on retinal image quality, plays an indirect role in emmetropization.
Retinal Components

- Acetylcholine (M1 or M4 receptors)
- Dopamine (Acs)
- Gucagon (Acs)
- Vasoactive Intestinal Peptide (Acs)
- Nicotine (Antagonist effects)
Atropine and FDM

Chronic atropinization prevents FDM in some species of monkeys.
Atropine produces cycloplegia by blocking the action of acetylcholine on muscarinic receptors in ciliary muscle.
Cholinergic Receptor Subtypes

M1  CNS, nerves
M2  Heart, smooth muscle, ciliary muscle
M3  Smooth muscle, exocrine glands, ciliary muscle
M4  CNS, nerves
M5  CNS, ciliary muscle

Atropine blocks all muscarinic receptor subtypes.
Effects of Muscarinic Agents on Form-deprivation Myopia
(Stone et al.)

![Bar chart showing interocular difference (mm) for different treatment regimens: MD control, MD + atropine, MD + pirenzepine (M1), and MD + 4 DAMP (smooth muscle).]

Blocking actions:
- **atropine** - all muscarinic sites
- **4-DAMP** - smooth muscle
- **pirenzepine** - neural ganglia
Atropine and pirenzepine are effective in preventing FDM in tree shrews. Other selective muscarinic antagonists (M2, gallamine; M3, P-f-HHSid) were not effective in blocking FDM. Hence, the M1 receptor appears to have potential therapeutic value. M1 blockers do not eliminate accommodation.

McBrien et al., 2000
Retinal dopamine is involved in FDM

Form-deprived Monkeys
(from Iuvone et al., 1989)

<table>
<thead>
<tr>
<th>Percent Change</th>
<th>Dopamine</th>
<th>DOPAC</th>
<th>Tyros. Hydroxylase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.5</td>
<td>-0.4</td>
<td>-0.3</td>
</tr>
<tr>
<td></td>
<td>-0.2</td>
<td>-0.1</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Form-deprived Eyes
(from Iuvone et al., 1991)

- MD alone
- MD + apomorphine (dop. agonist)
- MD + apo + haloperidol (D antagonist)
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.

Seltner & Stell, 1995
Choroidal Components

- Choroidal Retinoic Acid
- Choroidal Thickness
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.

Mertz et al., 2000a
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

Diagram:
1. Visual stimulus (Defocus?)
2. Retinal responses
3. Communication to sclera
4. Remodeling of sclera
5. Creep rate (fibrous) Growth (cartilaginous)
6. Axial elongation rate

Norton, 1999
Possible growth factors involved in FDM

Biochemical "stop" and "go" Signals

MD and bFGF
(basic Fibrobast Growth Factor)

MD and TGF-beta and bFGF
(Transforming Growth Factor Beta)

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.
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.

Guggenheim & McBrien, 1996
Decorin is the major proteoglycan in the marmoset sclera. The rate of proteoglycan synthesis is reduced in the posterior pole of FDM.
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.

Siegwart & Norton, 1995
Why Worry About Myopia?

• Myopia is common.
  – 36% of all prescriptions in USA.

• Myopia is expensive.
  – Total direct costs ($ billions) — estimated for 2000 in USA
    • $5 to $6 Spectacles & contact lenses
    • $1.6 to $1.9 Professional Services
    • $2.2 Refractive Surgery

• Inconvenience and complications of correcting strategies.
Ocular Sequelae of Myopia

Posterior Subcapsular Cataract
2 to 5 X

Idiopathic Retinal Detachment
4 to 10 X

Open-Angle Glaucoma
2.2 X

Chorioretinal Degeneration

(Curtin, 1985)
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.

Theoretical basis for traditional therapy
- Increased IOP
- Excessive convergence &/or accommodation
- Gravity & posture
Traditional Treatment Methods

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

Myopic children accommodate significantly less than emmetropic children for real targets at near distances.

Gwiazda et al, 1993
Do bifocals reduce the rate of myopic progression?

The Hong Kong Progressive Lens Myopia Control Study: Study Design and Main Findings

Marion Hastings Edwards, Roger Wing-hong Li, Carly Siu-yin Lam, John Kwok-fai Lew, and Bibianna Sin-ying Yu

Randomized, double-masked clinical trial to determine whether progressive addition lenses (SOLA MC lenses with a near addition of +1.50 D) reduce the progression of myopia in children over a 2 year period.
Longitudinal Changes in Refractive Error and Axial Length

At the end of the treatment period, the PAL group was on average 0.25 D less myopic.

Edwards et al., 2002

Mean ± SEM
A Randomized Clinical Trial of Progressive Addition Lenses versus Single Vision Lenses on the Progression of Myopia in Children

Jane Gwiazda,1 Leslie Hyman,2 Mohamed Hussein,2 Donald Everett,3 Thomas T. Norton,4 Daniel Kurtz,1 M. Cristina Leske,2 Ruth Manny,5 Wendy Marsh-Tootle,4 Mitch Scheiman,6 and the COMET Group7

Randomized, double-masked clinical trial to determine whether progressive addition lenses (Varilux Comfort Lenses with a near addition of +2.00D) reduce the progression of myopia in children over a 3 year period.
The Comet Study

Myopic Progression

Gwiazda et al., 2003
PALs reduce progression rate by about 50% (about 0.75 D in 3 years) in esophores with large lags of accommodation.
Do Near Adds Eliminate Accommodative Errors?

Subjects typically fail to relax accommodation by an amount equal to the add. Near adds may actually increase the degree of retinal defocus.

Rosenfield & Carrel, 2001
Does undercorrection slow myopic progression?

Undercorrection of myopia enhances rather than inhibits myopia progression

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Received 28 December 2001; received in revised form 14 May 2002

Randomized, controlled clinical trial to determine the effects of undercorrection on the rate of progression of myopia.
Methods

Subject Selection Criteria

• Age: 9-14 years.
• At least −0.5 D of myopia (sph equiv) in both eyes & myopic in all meridians.
• < 2.0 D of astigmatism in each eye.
• Corrected VA = 20/20 or better in each eye.
• No significant binocular vision problems.
• Normal ocular health.
• No previous contact lens wear.
Methods
Chung, Mohidin and O’Leary

• **Spectacle Corrections:**
  – **Full Correction:** Maximum plus to obtain best VA in each eye. *Full compliance 41 of 46.*

  – **Undercorrection:** Monocular VA maintained at 20/40 by undercorrecting by about +0.75 D. *Full compliance 40 of 47.*

• Patients instructed to wear spectacles at all times. *Full Compliance > 8 hours/day.*
Mean Changes in Refractive Error

The undercorrected group showed a greater rate of myopic progression.

Average sph equivalent (± SEM) for both eyes.

From Chung et al., 2002
The undercorrected group showed greater axial elongation.

No between group differences in corneal curvature, anterior chamber depth or lens thickness.

From Chung et al., 2002
The “CLAMP” Study
Contact Lens and Myopia Progression
RGPS vs Soft CLs

Walline et al., 2004
The “CLAMP” Study

Walline et al., 2004
The "CLAMP" Study

Walline et al., 2004
New Hopes for Optical Interventions

Emmetropization: Basic Operating Properties
Visual Signals for Axial Growth

Ferree & Rand, 1933

Refractive error varies with eccentricity. Myopes typically exhibit relative hyperopia in the periphery, whereas hyperopes show relative myopia in the periphery.

Mutti et al., 2000
Shift in Central Rx vs. Peripheral Rx

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

from Hoogerheide, Rempt, & Hoogenboom, 1971
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.

Uncorrected Myope

“Corrected” Myope

Optimal Correction?
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.

Jensen, 1991
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.
Shih et al., 1999

N = 200
Ages = 6-13 years
- 42-61% of treated children showed no myopic progression
- 8% of control group show no progression.
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
Long term Effects of Chronic Atropinization

Photo of adult cat that was treated with 1% atropine in the right eye from 4 weeks to 4 months of age.

Permanent alterations in pupil size, amplitude of accommodation, accommodation convergence interactions, neuropharmacology of intraocular muscles.
Pirenzepine Trials

• Safety and efficacy of 2% PRZ ophthalmic gel in myopic children: Year 1 (Siatkowski et al., 2003, 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

Siatkowski et al., 2003 (ARVO)
Tan et al., 2003 (ARVO)
Pirenzepine: Efficacy for Pediatric Myopia
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.

Siatkowski et al., 2004 (ARVO)
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?