

Nature vs. Nurture:

The roles of genetics and environment in the development of myopia

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Nature vs. Nurture

- Nature: There must be a genetic determination because so many studies show high correlations to the number of parents that are nearsighted and their degree of nearsightedness.
- Nurture: Environmental demands are the cause.

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Nature vs. Nurture (2)

- It is always BOTH!
- Two conditions must be satisfied:
 - 1. There must be an underlying physiological mechanism that is part of the human visual system that can alter the parameters of the physiology itself.
 - 2. There must be environmental triggers that activate the above named processes.

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It's Both!

- "The causes of myopia are not known. Epidemiological correlation suggest that lengthy periods of close work are probably a contributory factor, and that there is some genetic predisposition to myopia and its severity, with chromosomes 18q, 12p, 7q, and 17q having been implicated. Gene-environment interactions are being defined." ¹²

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Emmetropization

- Emmetropization is the process occurring during the normal growth period by which the eye changes from a state of ametropia to emmetropia.

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Active vs. Passive

- Norton, T., Siegart, J., "These experiments have provided convincing evidence that emmetropization in animals is an active regulatory process."
- Sorsby, "Ametropia results from failure of coordination of the optical components with the axial components."

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What structures change?

- It might be easier to ask what doesn't change? Nearly everything does.
- While the average eye is moving from moderate hyperopia to low hyperopia the eye is growing in axial length, the cornea and lens powers are decreasing, anterior chamber depth is increasing, etc. all in a controlled symphony of movement!

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Some Early Work on Physiology

- Ludlum et al. on the myopia research project done at the Optometric Center of New York.
 - 1964-69 develop testing devices
 - 1969-74 testing phase
 - Over 500 subjects seen every 6-months

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Ludlum Group Comparisons

Net Changes	Sub Group A (N=30)	Sub Group B (N=30)
Age	8.99 years	9.45 years
Keratometer	0.0348 D	0.0608 D
Refraction	0.0960 D	-1.5289D
Anterior Chamber Depth	-0.1848 mm	-0.2923 mm
Anterior Lens Radius	-0.3917 mm	-0.1749 mm

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Group Comparisons

Net Changes	Sub Group A (N=30)	Sub Group B (N=30)
Lens Thickness	-0.0157 mm	0.0032 mm
Posterior Lens Curvature	-0.366mm	0.0759 mm
Lens Power	-0.2823 D	0.0374 D
Posterior Segment Length	0.242 mm	0.7426 mm
Total Power	-0.4657 D	0.061 D

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Group Comparisons

Net Changes	Sub Group A (N=30)	Sub Group B (N=30)
Axial Length	0.4697 mm	0.7285 mm
Intra Ocular Pressure	-4.857 mm Hg	-4.782 mm Hg
Expected Myopic Shift (3x change in axial length)	1.4426 D	2.2031 D

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What effect does deprivation have?

- "When eyes are deprived of normal form vision they typically become axially elongated and myopic." ¹ (tree shrew)
- There are two periods of growth
 - Early period of fast change
 - Juvenile period of slow growth
 - "Eyes deprived of form vision early in the "juvenile" period became myopic, and had a thinner sclera and a reduced amount of collagen and proteoglycans than in control eyes." ³ (tree shrew)

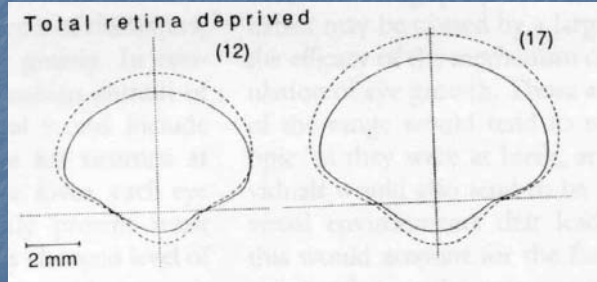
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Deprivation: Sector/Complete



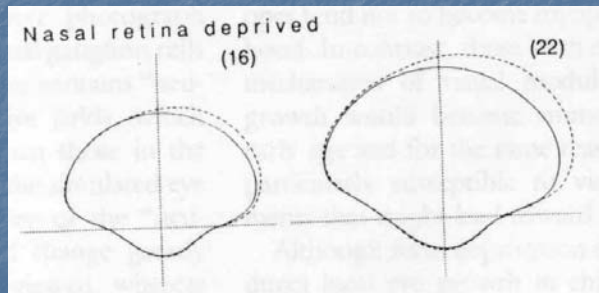
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Total deprivation 2 & 6 weeks



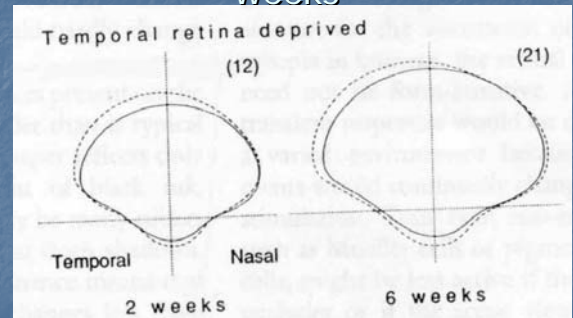
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Deprivation nasal: 2 & 6 weeks



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Deprivation temporal: 2 & 6 weeks



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Local or Higher Control?

- "In chickens, rhesus macaque monkeys, and tree shrews, deprivation-induced myopia has been found to develop even after the central communication from the retina was severed surgically or chemically." ¹
- "The amount of retinal blur may affect the quality or quantity of the retinal neural activity. This, in turn, may alter the release of dopamine, acetylcholine, or other neurotransmitters." ¹

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Local or Higher Control? (Hung and Ciuffreda)

- "Elongation occurs even when the optic nerve is severed." ^{A4}
- "Moreover, these appropriate changes in growth rate occurred even when the optic nerve was severed or the midbrain nuclei for controlling accommodation were lesioned, thus precluding any central or cortical visual feedback mechanism. Hence, the retina is the site for controlling the rate of axial length growth." ^{A5}

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Newer Concepts of Physiological Mechanisms of Change

- Emmetropization
 - Selective tuning of the components of the optics as the system matures.
 - Many changes occur in infants with shifts towards a low degree of hyperopia over the first 2 years of life. The further from +0.75 the faster the shifts occur.
- Retinal defocus/local hormone/enzyme release

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Human Refractive Trends⁵ (Yackle/Fitzgerald)

- Sphere: Born $< +2.50$ => emmetropia
- Sphere: Born $> +2.50$ => increase hyperopia until age 3.5
- Cylinder: at birth average 2.98 diopters! By 2.5-5 years of age decreases to about 1.00D.
- Ametropia: Infants lose 1/3 of their spherical equivalent and 2/3 of their astigmatism by age 2!
- Aniso: 3.00 D or more of aniso: 90% chance of staying aniso by the age of 10. 60% are at risk for amblyopia!

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Scleral Thinning: an early or late change?

- "The eye enlargement is accompanied by scleral thinning, which occurs early in the development of myopia and which is due not to passive stretching but to tissue remodeling. A later feature is a reduction in the diameter of the scleral collagen fibrils, which further weakens the sclera."¹²

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Some Cellular Biology

- "The fibroblasts secrete collagen, the main structural component of the sclera. During the development of myopia collagen degradation is accelerated and collagen synthesis is reduced."¹³

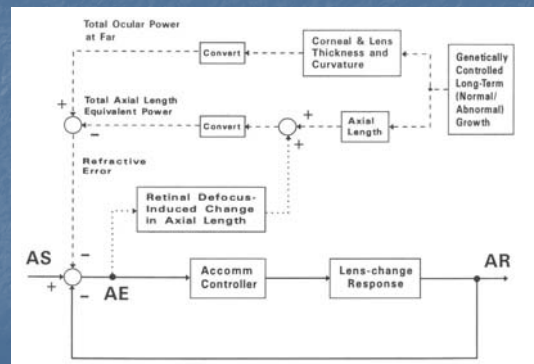
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Hung and Ciuffreda Statements of Principle

- "It is somewhat ironic that rather than being a failure of the emmetropization process, myopia development is actually a result of the emmetropization process that operates under the constraints of the AS/R (Accommodative Stimulus/Response) function during increments of genetically-programmed ocular growth."¹

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Hung Ciuffreda Simple Model



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Complex Model

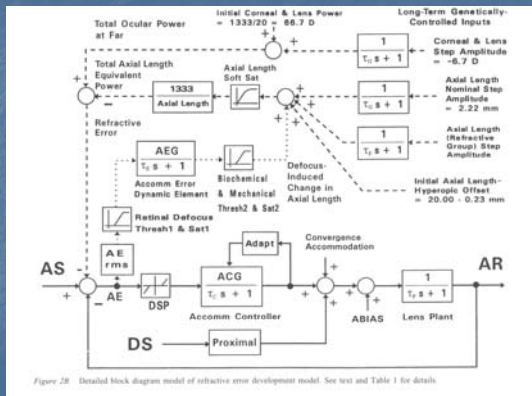


Figure 28 Detailed block diagram model of refractive error development model. See text and Table 1 for details.

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Retinal Defocus Pathways & Scleral Growth

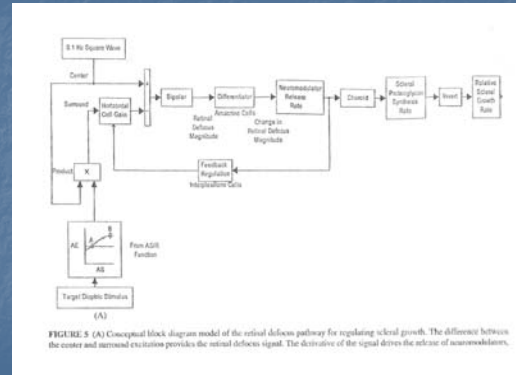


FIGURE 5. (A) Conceptual block diagram model of the retinal defocus pathway for regulating scleral growth. The difference between the center and surround excitations provides the initial defocus signal. The derivative of the signal drives the release of neurotransmitters.

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What Makes it Work?

- “During an increment of normal genetically-driven axial length growth, the magnitude of retinal defocus will have decreased or increased, respectively. It is proposed that feedback regulation provided by the interplexiform neurons from the inner to the outer plexiform layers, which aims to maintain a relatively constant sensitivity to retinal-image contrast, leads to a decrease or increase, respectively in neuromodulators, such as dopamine.”²

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More Gene Stuff

- “Gene expression of matrix metalloproteinases (MMP’s) and their tissue inhibitors are both increased during development of myopia, which indicates tight control of collagen degradation.”¹²

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Muscarinic Receptors

- "Muscarinic receptors are found on virtually every type of fibroblast. In cultured human scleral fibroblasts the muscarinic antagonist atropine, and to a lesser extent pirenzepine, reduce proliferation whereas the agonist carbachol increases it slightly. Yet antagonists can slow the progression of myopia." ¹²

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Gene Switching

- "The same gene can be reused in different places and at different times simply by putting a set of different promoters by it." ¹⁴
- "To make grand changes in the body plan of animals, there is no need to invent new genes. All you need to do is to switch the same ones on and off in different patterns. Suddenly, here is a mechanism for creating large and small evolutionary changes from small genetic differences." ¹⁴

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Gene Switching (2)

- Frenchman François Jacob and Jacques Monod discovered in the 1950's how this switching occurs.
 - "Known as promoters and enhancers, these switches are the key to the development of a body from an embryo. Many genes require several activators to attach to their promoters; activators can work in different combinations; and some genes can be switched on by different sets of activators." ¹⁴ ...

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Gene Switching (3)

- "... The result is that the same gene can be used in different species or in different parts of the body to produce completely different effects depending on which other genes are also active." ¹⁴
- "Suddenly, here is a very different way of viewing genes: as a set of developmental switches. All tissues carry the complete set of genes, but the genes are switched on in different combinations in different tissues. Now forget the sequence of the gene; what counts is where and how the gene is expressed." ¹⁴

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A final thought on genes

- "Genes are devices for extracting information from the environment. Every minute, every second, the pattern of genes being expressed in your brain changes, often in direct or indirect response to events outside the body. Genes are the mechanisms of experience."¹⁴

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OK, So I have a different gene, does that mean I'm doomed?

- "Development accommodates to the environment: it is capable of coping with different circumstances and still achieving a result that works. If different developments can result from the same set of genes, then different genes might also be capable of achieving the same outcome. Technically one can say, development is well 'buffered' against minor genetic changes."¹⁴

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Conjecture on Mechanism

- Wallman et.al. suggest that THE problem is deprivation of form vision.
- They suggest that reading is a type of form deprivation in that it does not provide adequate amounts of differences in the person's peripheral vision from fixation to fixation.
- This results in a relative global form deprivation, in spite of massive use of the central aspects of vision for decoding.
- The lack of stimulation causes a lack of neuronal activity in the peripheral nets.

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Conjecture on Mechanism (2)

- The lack of neuronal activity may then be linked to lack of use and transport of essential nutrients and the retina functions "as-if" it is visually deprived.
- Thus, the natural elongation that occurs in the form deprived conditions continues unabated.
- Luminance: paper has only a 10 times light ratio differences between the letters and the background. Normal outdoor scenes have many orders of magnitude differences more.

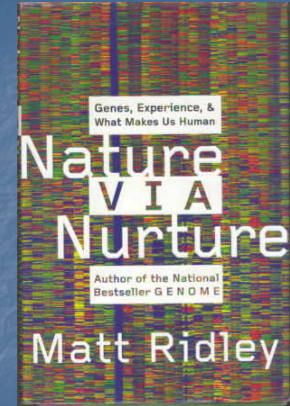
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Conjecture on Mechanism (3)

- "Some children may chronically under-accommodate while reading or performing other near work. If so, they may experience a situation similar to tree shrews reared with minus lenses, where an intact emmetropization mechanism produces an elongated eye because the focal plane is shifted posteriorly, increasing the amount of blur and triggering elongation."

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Nature via Nurture



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