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THE PATRICIA LANCE LECTURE

The next fifty years in Orthoptics and Ocular Motility

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Abstract

To predict what may develop fifty years ahead for ocular motility and orthoptics we must look at current areas of experimental interest: neurophysiological modelling of visual processing, developmental aspects of strabismus/amblyopia, and chemo-therapy among others. As modelling of the visual system proceeds, one may anticipate that it will soon be necessary to test concepts of normal processing in abnormal situations such as strabismus or visual deprivation. We can expect to see emphasis upon psychophysical testing of all types of visual functions in the very young child as well as attention toward visual plasticity in adults. Such testing will involve increased use of electrophysiology as well as the development of additional clinical tests. I predict that the role of the orthoptist will expand to encompass these new areas of diagnosis and documentation.

Key Words: *Strabismus, Amblyopia, Neuro-plasticity, Neuro-chemical, Orthoptist*

THE NEXT FIFTY YEARS IN ORTHOPTICS AND OCULAR MOTILITY

It is indeed an honour to be invited back to Australia, especially on the occasion of this, your 50th anniversary. To be asked to be the 4th Patricia Lance Lecturer is a very humbling experience. Not only do I have the greatest respect for Patricia Lance herself and her work, but the previous Lance Lecturers have set the highest standards.

The research and technological advances of the past decade certainly point toward remarkable potential for future development in motility and in orthoptics. I can see great strides toward opening some of the "black boxes" of ocular motility and strabismus, such as the etiology, heredity and genetics of strabismus; defining and expanding plasticity of the visual system, including further studies on suppression, amblyopia and other sensory disorders of strabismus. I also expect to see great strides in both surgical and non-surgical treatment of strabismus and amplyopia.

FROM SINGLE CELL PHYSIOLOGY TO MACRO SYSTEMS

Inner Image

If we have thought about visual processing at all, the most frequent analogy is that of a camera and film. The retina performs the function of the camera with its inverted image and

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the brain or visual cortex serves as the film or "inner screen". While such a model has heuristic value it does little to advance our knowledge nor does it help us know what object we are looking at or its shape, texture, depth, color size or spatial relationships.

Simple image or photographic representation is often deceptive, as we know from multiple examples of visual illusions such as Frazier's Spiral (Fig. 1). It is almost impossible to

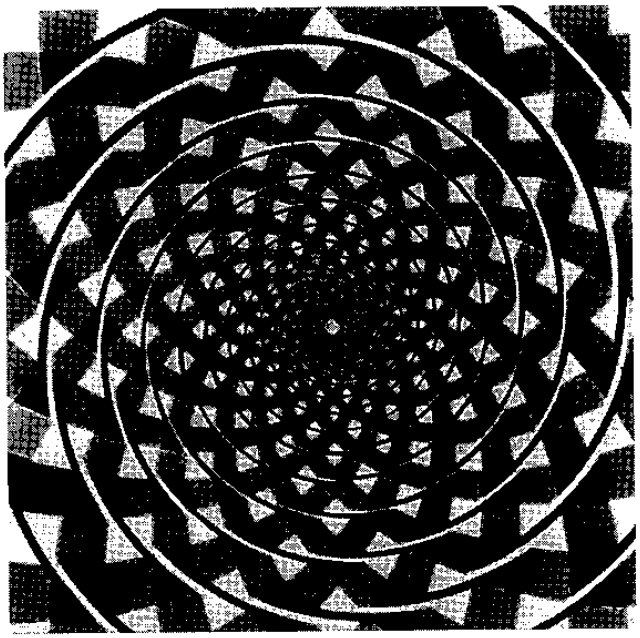

Figure 1. Frazier's Spiral is a popular illusion in which the eye is decieved into believing a true spiral exists.

convince individuals that there is no spiral in this two dimensional figure. The illusion of a spiral effect is so strong that even when subjects are asked to use their finger to follow the lines, they automatically move their finger inward in a spiral direction when no such spiral exists.

The human visual system can be fooled but it is much too sophisticated for it to happen often or easily as would happen on an "inner screen" model of vision. Nor does the inner screen model assist in explaining defects of vision such as strabismus, nystagmus or amblyopia.

SINGLE CELL PHYSIOLOGY

It has been since the epochal studies of Hubel and Wiesel in 1959[1] that the most dramatic advances have been made in our knowledge of how the brain converts an image in visual space to a perceptual concept of that image. The work of Hubel and Wiesel, Kuffler, Mountcastle and others (for a review see Schiller[2]) together with breakthroughs in electro-recording techniques and micro-electrodes have begun to break visual processing down into single-cell activities.

There are more than 160 million receptors in the human eye and the output of the whole receptor mosaic can be thought of as equivalent to a grey level description with each receptor providing one pixel.[3] Each receptor influences not just one brain neuron but hundreds of thousands. The grey level measurement provided by each receptor is used over and over again by many brain cells all working together in parallel. Color information is transmitted by the differential responses of receptors to certain wavelengths and inhibition by others. Specialized cells in the visual cortex respond to orientation, movement, or length, while others are more sensitive to particular spatial frequency patterns. Cortical cells have been found that respond to information from one or the other eye, either eye or both simultaneously. Disparity cells are responsible for stereoscopic coding with some cells responding only to nasal disparity producing the perception of distance stereopsis and other cells responding only to temporal disparity coding an awareness of "nearness" in the three dimensional array. Discoveries of behaviour patterns and cell types continue in animal models and are often supported by psychophysical studies in humans.

This is an exciting time in vision research. The challenge of the future seems to be to organise known single cell activities into systems and sub-systems of vision processing. In strabismus, the task is to relate strabismic entities and their sequelae to specific behavioural deficits and to changes in identified subsystems of the visual machinery.

MAGNO/PARVO CELLULAR

An example of this type of approach can be seen in current models of visual processing which assigns certain functions to proposed

anatomical pathways. Cells from the retina to the cortex can be divided into two functional categories serving visual perception, parvocellular and magnocellular[4,5,6,7] (Fig. 2). Cells

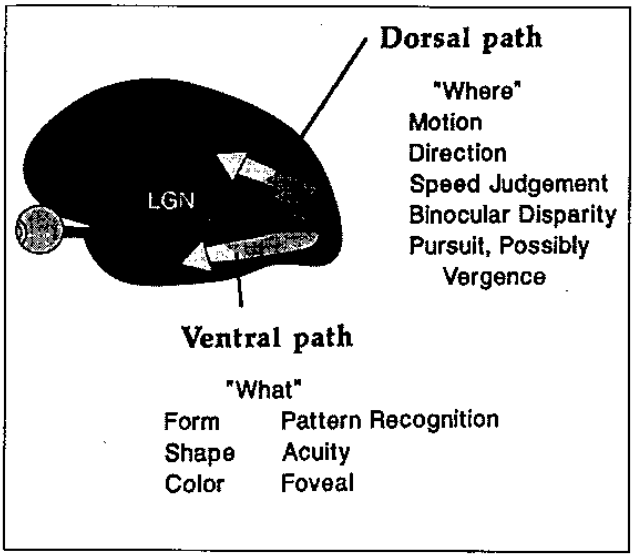

Figure 2. Model of the magnocellular ("where") and parvocellular ("what") paths of visual processing.

within the parvocellular system, the "what system", respond best to high spatial frequency patterns, with slow or no movement. The parvocellular system is largely composed of cells from the foveal area and projects through to the striate cortex then on to visual area 2 and to cortical area MT. The parvocellular system is colour sensitive and is responsible for high resolution vision. This is the system believed to be most involved in amblyopia.

The magnocellular system is composed of large cells with rapidly conducting fibres from the peripheral retina and responds best to moving stimuli and low spatial frequency patterns. This system projects through the two ventral layers of the LGN to the striate cortex and on to visual area 2. This system also has projections to the superior colliculus, that portion of the mid-brain that is so important for ocular movements, especially reflex ones. It is felt that the magnocellular system is responsible for processing motion, vergence control, stereopsis and may play a pivotal role in the etiology of infantile strabismus.[8,9,10] This system is color blind.

OKN

Incrimination of the magnocellular system in strabismus was prompted by asymmetrical optokinetic nystagmus (OKN) which is characteristic of infants to about age three months. The response to objects moving in a temporal to nasal direction is more brisk than for nasal/temporal movement. Binocular OKN's are symmetrical. In infants with infantile strabismus, the asymmetry often persists and is frequently associated with latent nystagmus and dissociated vertical divergence. Some investigators suggest that loss of cortical binocularity and binocular input to a hypothetical "movement system" is the cause of the OKN deficit. Others suggest that maldevelopment of the visual movement system may be the etiology of infantile strabismus.[8,9,10] It is interesting that the magnocellular system is believed to reach mature levels of function at about the same age that binocularity, vergence control and stereopsis are developed in the infant.

Although the Lateral Geniculate Nucleus (LGN) is the main target of ganglion cells, there are at least 9 other nuclei within the brain which receive direct retinal input[11]. All told, the number of neurons allocated to sensory visual function composes approximately 65% of the cortex. Indeed the visual system seems to be the most highly evolved of the brain structures with multiple parallel paths, the function of most of which is largely an enigma.

The role of researchers in the future will be to determine the purpose of these systems and their component parts. This will involve clinical and psychophysical investigation of visual processes not currently considered such as movement and contrast sensitivity, spatial sensitivity, color, and all in combination. Anatomical confirmation will perhaps be possible with some of the new generations of imaging equipment now becoming available such as Positron Emission Tonography, Magnetic Resonance Imaging and others yet to be developed. Patients will be studied in the context of what changes have occurred in specific subsystems to cause the types of behaviour and sensory deficits.

POSITRON EMISSION TONOGRAPHY

Positron Emission Tonography (PET) shows a great deal of promise toward allowing investigators to correlate anatomical areas with function. In a study in which 50 children with significant closed head injury were evaluated, cortical blindness was the most frequently found ocular problem. PET scanning was performed during the rehabilitation of 13 of these patients who suffered traumatic brain injuries with cortical blindness.[12] The presence of metabolic activity in the visual cortex was found to accurately predict which children would recover some form of vision at the time of discharge. PET studies have indicated the ability to detect the areas of the brain that are being used for activities such as reading, judgment of velocity and speaking. The hope is that over time, PET techniques will enable investigators to discriminate normal from abnormal behaviour in many aspects of visual function.

DEVELOPMENTAL FACTORS AND VISUAL PLASTICITY

Normal Visual Development

An area that has made remarkable advances in the past two decades is our knowledge of normal visual development. While much has yet to be learned, we are beginning to acquire some fairly firm estimates of when many visual skills are acquired and to establish a normal range of function for others. After two decades of psychophysical and electro-physiological studies, the evidence is compelling that virtually all aspects of spatial and temporal vision are deficient in normal infants until several months after birth. Various functions appear at different points in development suggesting processing by parallel systems which develop at different rates. For example, visual acuity does not reach mature levels until 2 to 3 years when tested by preferential looking techniques but more rapid gains in acuity are recorded by Visual Evoked Potential (VEP) testing. Crowded visual acuity is not mature until age 10 years. Binocularity as evidenced by vergence responses, binocular summation with VEP and aversion to rivalrous stimuli occur during the third to sixth month. Stereopsis develops between 5 and 7 months but we do not know when these functions reach their mature levels.[13]

It is apparent that the period between 3 and 7 months is critical for visual development. It is known that the infant visual system is susceptible to insult during this time and any insult can manifest itself by strabismus, amblyopia or nystagmus. Nor is the child safe after a process has reached mature levels. Sensory adaptations such as amblyopia can occur at any time during the plastic period of visual development which in some children persists until age 12 years. So the point at which a function is "mature" does not signal the end of changes in response to environmental factors.

An understanding of the factors controlling visual plasticity is essential to the future development of improved programs of treatment of strabismus and the sequelae of strabismus. It is only during the plastic period of visual development that adaptations such as abnormal retinal correspondence (ARC), suppression, and amblyopia are developed. To date our success in eradicating these anomalies has also occurred during this plastic period.

NEUROCHEMICAL ALTERATION

Future research will be devoted to finding ways in which the plastic period can be prolonged or reversed. Various types of anti-inhibitory drugs are likely approaches. In animal models GABA-receptor blockers, catecholamine depletion and norepinephrine have all shown promise in reversing certain aspects of amblyopia and in enhancing cortical plasticity.[14] In a recent study on human strabismics, the administration of Levodopa was successful in increasing contrast sensitivity and reducing the size of the suppression scotomas in amblyopic eyes.[15]

In addition to using L-dopa in amblyopic subjects, the drug has been administered to normal subjects.[16] In all cases, the Dopaminergic drug induced an improvement of contrast sensitivity in the range of medium to high spatial frequency, that is, above 2 cycles per degree.[17] Another study used Levodopa in 5

older amblyopic children who had failed to respond to conventional occlusion therapy. One hour after drug ingestion, Snellen visual acuity temporarily improved as did contrast sensitivity and pattern VER's. This improvement was noted in both dominant and amblyopic eyes. The improvement in visual function started to decrease 5 hours after drug ingestion.[18] In another study of amblyopia, Levodopa was used for one week of daily administration in a cross-over, double-masked design. Fixation scotomas decreased in size and visual acuity improved in 70% of patients treated with Levodopa. This improvement lasted for at least four weeks after the drug was discontinued. Authors in both studies reported side effects including emesis and nausea. These are early pilot studies of the use of only one drug in human subjects and as such are extremely exciting. I would like to suggest that in the future a combination of drug therapy and rehabilitation could be used to both shorten the time needed to improve amblyopia and perhaps prolong or extend the plastic period to the point that improvement in amblyopia and strabismus could be obtained in even older individuals.

ADAPTATION: A FORM OF ADULT CORTICAL PLASTICITY?

Essential to any future manipulation of plasticity, whether it be by drugs or rehabilitation, is a better understanding of the critical period and the plastic period of the human visual system. At one time, cortical plasticity was viewed as changes or adjustments in the anatomical connection patterns that make up the visual pathways. The effect of experience on visual processing was largely ignored in this definition of plasticity. However, it was found that visual deprivation decreased cortical connections from the deprived eye. Surgery to rotate the globe in fish and amphibians caused abnormal ganglion connections to develop. Removal of one eye in an animal caused abnormal projections from the other. It was determined that sensory experience could affect connection patterns. Thus, it became important to study the possible role of adaptive shaping of such patterns. The prevailing view of a rigidly genetically determined connection pattern was abandoned. Plasticity is now considered as the capability to make functionally appropriate adjustments in the anatomical connection patterns (neuro-chemical and neuronal connectivity) that compose the visual pathways. There are many lines of evidence to suggest that cortical plasticity or adaptation to the environment can cause major perceptual changes. Whether this exemplifies cortical plasticity in the classical sense remains to be seen.

AFTEREFFECTS

Visual Aftereffects are phenomena used by psychophysicists to study populations of visual cells acting together. Aftereffects, and in particular contingent aftereffects, strongly suggest that visual plasticity persists into adulthood. A typical aftereffect consists of a technique whereby an attribute is measured on a test pattern. The observer then views an adaptation stimulus for a period of time and is retested on the original test pattern and the attribute remeasured. The McCollough aftereffect is a contingent aftereffect that suggests adaptation of cortical elements can lead to long term alteration in perceptual attributes. Figure 3b is a typical test slide of the McCollough effect, consisting of achromatic gratings of a given spatial frequency. An individual is tested on this slide to make sure that the gratings at all orientations appear achromatic. Then the subject adapts to orthogonal red and green grating of the same spatial frequency as the test grating (Fig. 3a). The subject is instructed to look from one test grating to the other so that

Figure 3a. Red Vertical and Green Horizontal McCollough Adapting Pattern, Adapting Pattern is viewed for 3 minutes.

the stimulus is temporally interrupted. After a period of perhaps 3 minutes when the subject looks back at the test grating, it may now seem tinged with colours complementary to the adaptation grating (Fig. 3b). That is, if the subject

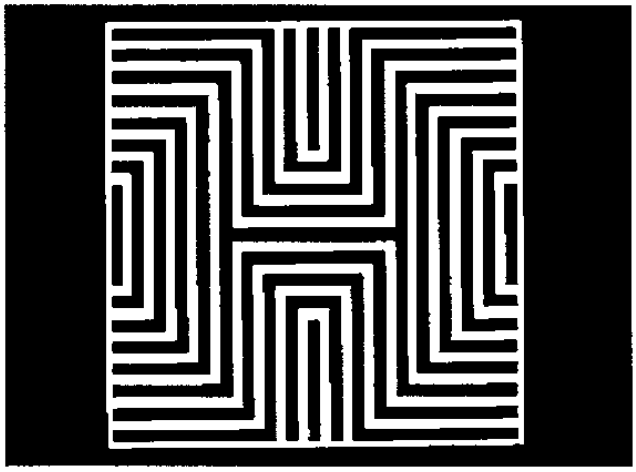

Figure 3b. When the Achromatic Pattern is viewed after adaptation, the vertical lines will appear faintly tinged with green and the horizontal lines will appear pink. The aftereffect can persist for 30 days.

viewed red vertical gratings, the achromatic vertical gratings will appear green. If the adaptation grating was of green horizontal gratings, the horizontal gratings will be faintly tinged with pink. This obviously is reminiscent of an afterimage with which Orthoptists are so familiar. However, there are many attributes of the McCollough Aftereffect which make it totally unlike an afterimage and which implicate a neural model of cortical plasticity or perceptual learning.

First, an afterimage is always associated with a particular area of the retina. In other words, if you adapt to a brightly colored circle, the afterimage will be a circle and will obey Emmert's Law in that the further away the subject looks the larger the circle seems to be. The afterimage is based on fatiguing of photoreceptors in the retina and is retinospecific and lasts for seconds. The adapting gratings for the McCollough effect were simply large rectangles, and the test grating had a totally different shape. The McCollough effect is contingent upon the spatial frequency of the lines in the test grating and is not retinospecific. There are many other differences but the most significant one is that the McCollough Effect is extremely long lasting. After 10 or 15 minutes of adaptation, a McCollough Effect can be elicited from subject 30 to 45 days later.

Obviously this can not be attributed to fatigue. It seems to be more efficient to view the McCollough Effect as a form of perceptual learning in the Hebbian sense, such that along certain synaptic pathways there is a predisposition toward facilitation of synaptic connections produced by repetition or adaptation. These synaptic pathways are believed to be the antagonistic colors and orthogonal gratings. During McCollough adaptation, synaptic paths are established and reinforced, linking color with orientation. There is some neurophysiological and psychophysical evidence that orientation specificity is not a product of excitation but of inhibition. It is unlikely to matter to the nervous system whether a signal is inhibitory or excitatory, thus the Hebbian synaptic modification can occur via inhibitory synaptic connections linking orientation with the opponent inhibitory process of the adapting color.[19] In support of this view, I found that certain neurochemical alterations such as caffeine can decrease the McCollough Effect as can sleep deprivation. In another series of studies which I performed, I found that subjects with suppression or amblyopia had exaggerated McCollough Effects in the amblyopic or suppressed eye.[20] The reason for bringing up the McCollough Effect in this discussion is not simply because it is a fascinating contingent aftereffect, but because it is an excellent example of a phenomenon which can be produced in adult subjects implicating perceptual learning or cortical plasticity.

THE TILT AFTEREFFECT

The tilt aftereffect is a second example of what may be considered cortical plasticity which can be elicited in normal adults causing a modification of perception after adaptation. Figure 4 is the testing grating which should appear perfectly vertical. Then one adapts to a tilted grating, tilted to the left for a certain period of time (Fig. 5). After looking at this grating for about 45 seconds, when one looks back at the

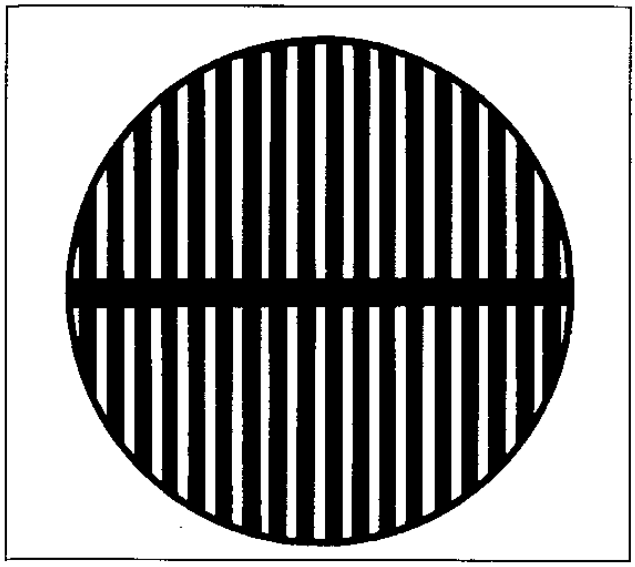

Figure 4. Tilt aftereffect test grating.

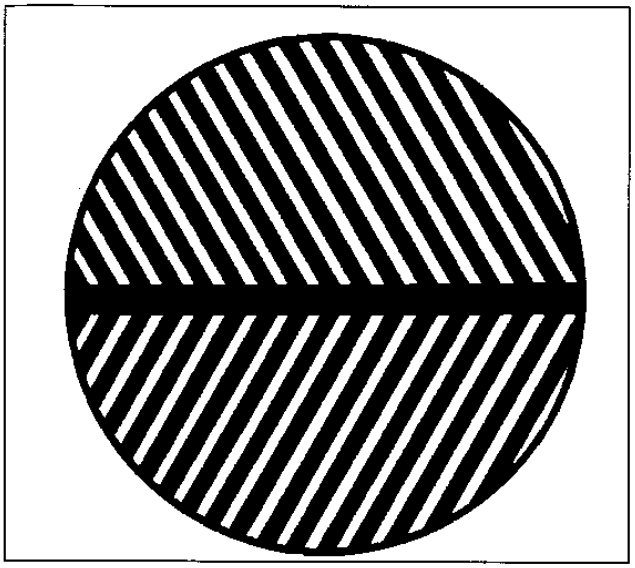

Figure 5. Tilt aftereffect Adaptation grating. After 1 minute of staring at leftward titled lines, when Fog. 4 is again viewed, the vertical lines will seem to tilt to the right before straightening.

vertical test grating, the grating for a fleeting instant will seem to be tilted to the right and then will straighten up. With prolonged viewing of a tilted grating, there is a much longer aftereffect and, in fact, the aftereffect can be appreciated weeks after the original adaptation.[21]

Gisbon, in 1937, studied subjects' ability to judge the verticality of luminescent rods in a darkened room. He adapted subjects to a tilted environment through tilted mirrors or through a peephole at a tilted room. After prolonged adaptation, when subjects were asked to judge verticality, they systematically misjudged the objective vertical for long periods of time. Additional experiments in years past have studied patients wearing inverting prisms. After wearing these prisms, which reversed right and left or up and down, for up to a week or so, subjects were able to readjust their perception to the point that things again seemed "right side up". They were able to ride bicycles, eat, read, and function normally after just a few days of adaptation. When the prisms were removed, they had to readjust. The major question is whether this is an example of cortical plasticity or whether subjects were making cognitive adaptive changes.[22] I would like to present two case histories of patients which present us with exactly that question. Both of these patients also represent an example of what I think will be some of the innovative surgical approaches of the future.[23]

CASE HISTORIES

Mr. C. is a 77 year old male with age-related maculopathy causing him to have visual acuity in his right eye of 2/200 and in the left eye of 20/50. Two days before admission, Mr. C. had a sudden decrease in visual acuity in the left eye to 2/200 caused by a massive subretinal haemorrhage. Fig. 6 shows the left eye before surgery. Mr. C. was admitted for a surgical procedure in which the macula area was moved into a healthy area of retina with normal retinal pigment epithelium. The sub-retinal area was injected with fluid creating a total retinal detachment. A 360 degree retinotomy was

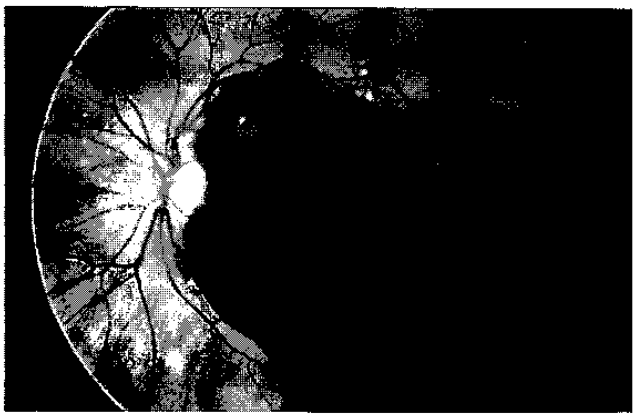

Figure 6. Pre-operative retina photograph of Patient 1.

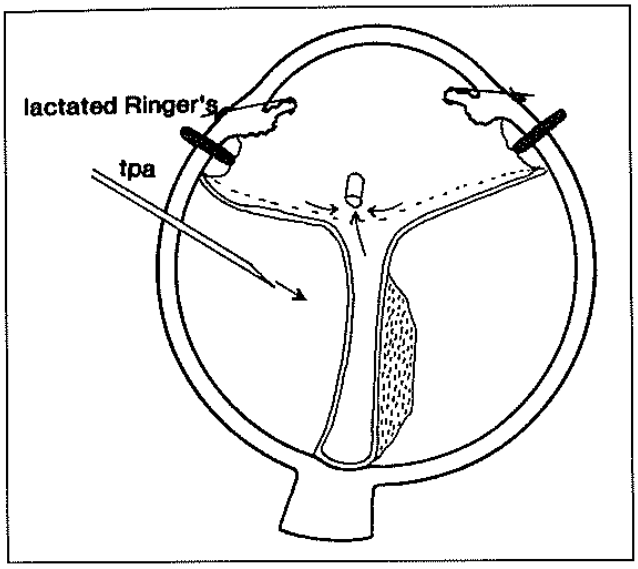

Figure 7. Macula Relocation surgery. The sub-retinal space is injected with air.

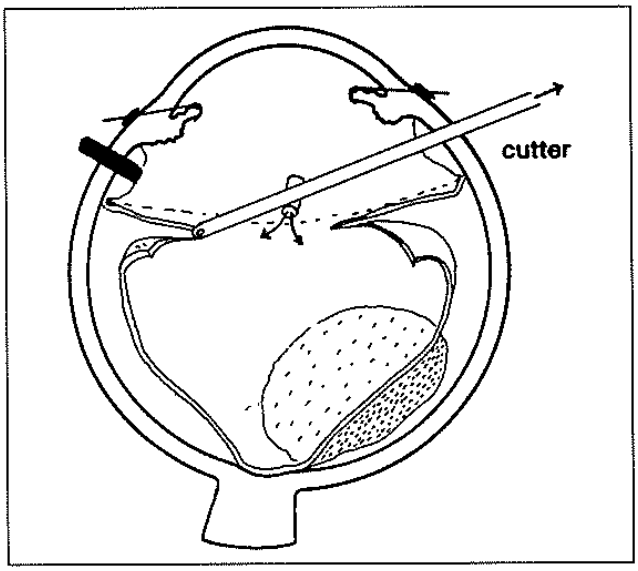

Figure 8. A 180° retinotomy performed.

performed and the entire retina rotated around the optic nerve so that the macula was moved upwards 45 degrees relative to the optic nerve (Fig. 7,8,9). The retina was reattached and silicone oil used to retain the retina immediately post-operatively so that visual acuity in the eye remained poor for several months after the procedure. Once the silicone oil was removed, the visual acuity gradually improved. Fig. 10 is a post-operative photograph of the eye. As visual acuity became acute, Mr. C became very aware of cyclo-torsion as well as past-pointing and displacement of objects of regard.

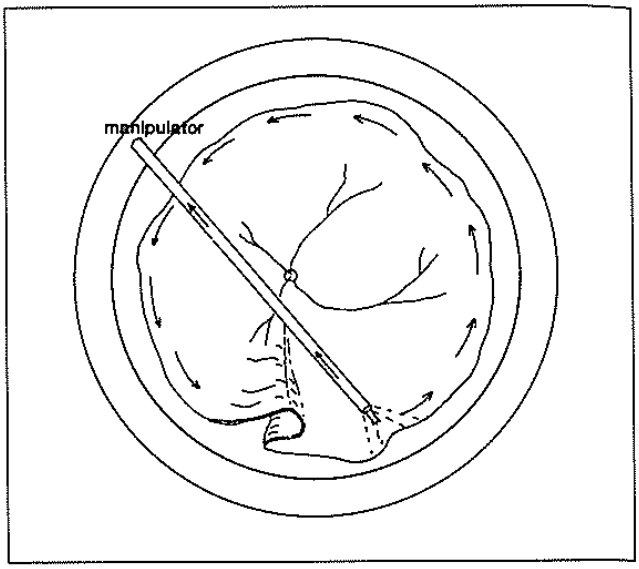

Figure 9. The macula is rotated about the optic nerve to a new area of healthier retina.

After 8 months the vision in the affected eye was 20/125 and this was by far his better eye. At near he could read 20/60 words. However, he was quite aware of subjective excyclo-torsion of the image approximately 45 degrees with a Maddox rod. He had complete inversion of his OKN response so that when the drum was

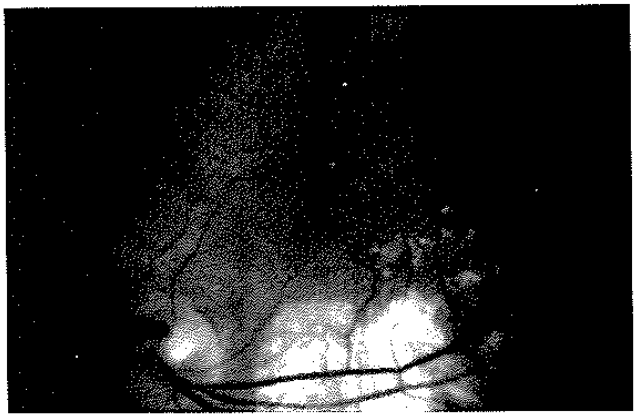

Figure 10. Post-operative photography with macula rotated upward 45°.

rotated vertically, he demonstrated a horizontal movement, and vice versa on horizontal drum rotation. Mr. C was advised to patch his right eye in order to use the eye with the macula relocation as much as possible. Over time, the torsion became variable so that a vertical image was seen to be upright and perfectly vertical. A horizontal image varied 10 to 15 degrees from horizontal. He found that he was

able to watch television and read much better but he still had a great deal of difficulty with eye-hand coordination tasks and especially walking. A planned strabismus procedure to cyclotort his eye was delayed and he was encouraged to use the eye in an attempt to see if he could further adapt and become less aware of the cyclotorsion and proprioceptive problems. At his last exam, 14 months post-operatively, his vision was 20/80 -2 at distance and 20/60 at near. On alternate cover test he measured an Exotropia of 50 and a Right hypertropia of 40. Prism placement did not alleviate his proprioceptive problems. He had no torsion on the vertical or horizontal meridian monocularly but binocularly would still fix with his unoperated right eye and was aware of a tilted "film" over his field of vision. He continued to demonstrate OKN inversion.

A second patient was a 76 year female with hand movement vision in the left eye due to AMD. The right eye had 20/200 vision until ten days before admission, when the vision suddenly decreased and the patient was unable to read secondary to a massive sub-retinal haemorrhage. Figure 11 depicts the pre-operative retinal status, and Figure 12 the post-operative status of the eye after the macula was moved downward 25 degrees into a healthy area of retina. After 4 months, the vision in the right eye was 4/200 and at near was 20/200. The patient was subjectively aware of incyclotorsion of objects of 25 degrees. She also demonstrated OKN inversion. She was encouraged to use the eye with the macula rotation. After 6 months when she returned, her vision was 15/200 in the right eye and she reported that images no longer appeared to be cyclorotated. Despite the fact that she no longer subjectively noted torsion, she still showed OKN inversion. She also had a tendency to past-point on eye-hand coordination tasks, but she felt that this was beginning to improve as well.

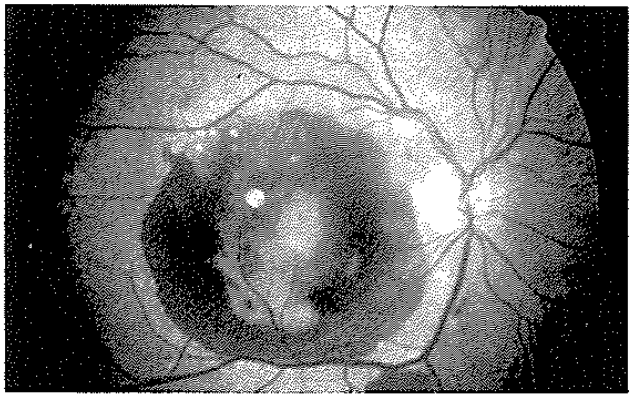

Figure 11. Pre-operative photography of macula haemorrhage in Patient 2.

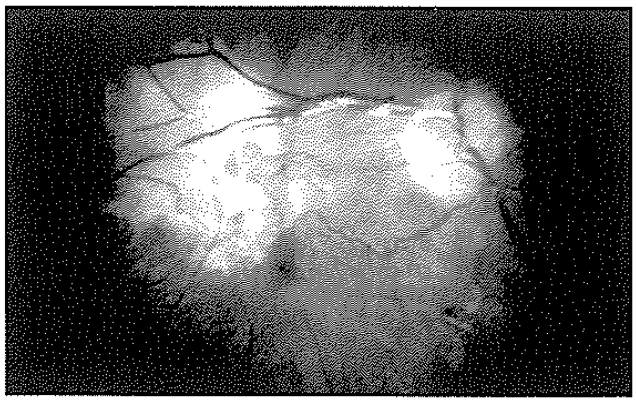

Figure 12. Post-operative photograph of Patient 2 showing macula rotated downward 25°.

In both patients, with use of the torted eye, subjective cyclo-torsion decreased. Proprioceptive anomalies persisted as demonstrated by OKN inversion and past-pointing. The big issue is whether the slow adaptation that these patients made to their altered motor state is a form of cortical plasticity. It is essential that in the future we gain greater understanding of the mechanisms especially the neuro-chemical ones, underlying plasticity including adult plasticity. This might allow for the development of techniques to stimulate these plastic responses in the visual system in both children and adults. Perhaps in conjunction with neuro-chemical therapy the binocular system could be rehabilitated and binocular cells of the cortex reactivated by appropriate visual stimulation.

REVERSAL OF THEORIES

The next fifty years will be a testing ground for many "pet theories". Some will hold up under challenge and others will be replaced. Some of the models that I have suggested in this paper will perhaps not last through the next decade. That is not important. What is important is that

we are now beginning to look past the mechanical "eye turned in, straighten it" thought process into the neuro-mechanisms which presumably could be the etiology of strabismus. Proprioception may indeed be found to play a role in ocular alignment. The accommodative convergence to accommodation ratio may not be fixed and innate but may be proven to be an adaptive and plastic mechanism like many others. If so, approaches to alter it may play a role in treatment. Indeed, neuro-plasticity may be discovered in several systems and ways found to use this adaptability to normalise visual function.

ROLE OF THE ORTHOPTIST

Where will the orthoptist be in the future? I foresee a need for an academically based visual specialist who has a broad understanding of the mechanism of vision, visual development and furthermore who has the clinical skills to apply this knowledge in the evaluation and treatment of patients. I predict that treatment will play a larger role in the future of ocular motility. Such treatment will not only include surgical techniques but advanced non-surgical approaches will be developed and neurochemical approaches may facilitate both. Foremost among these will be treatment to enhance binocularity and effective amblyopia treatment. The orthoptist has demonstrated resourcefulness and adaptability in the past 50 years. That trait will continue to serve the profession. The orthoptist will be the person who administers treatment and evaluates success. Likewise, the orthoptist will be the person who initiates early screening not for amblyopia, but for strabismus within the early, developmentally critical months of a child's life.

To fulfil such a role in a technologically complicated setting could reasonably require a stronger academic base perhaps even in a post-graduate setting. This would only follow trends present in other health care professions and in other countries. Australia has taken the lead in the world in this respect and is to be congratulated. It makes sense to have a clinically based post-graduate program but with the potential for some persons to continue into a more research oriented career involving perhaps a Ph.D. Knowledge in the area of ocular motility is growing at an astounding rate. The orthoptic profession can play a contributing role in the continued expansion of this field as a competent and educated clinical investigator and observer. I challenge you to approach the future with the same enthusiasm and excitement that I have always associated with Patricia Lance. May the next fifty years be the best to come!

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