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CITY UNIVERSITY LONDON

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ON THE AETIOLOGY OF MYOPIA

Aspects of Structure, Function and Epidemiology

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BSc(Hons); PhD; FCOptom; FAAO

Doctor of Science

CITY UNIVERSITY

July 2015

CONTENTS

CURRICULUM VITAE (Summary)

PROFESSOR B. GILMARTIN PhD, BSc, FCOptom, FAAO. July 2015

BSc(Hons) degree in Optometry (First Class) City University 1968. Fellowship, College of Optometrists (FCOptom) 1969, (Life Fellow awarded 2000). General Optical Council (GOC) registration, 1969. Lecturer (City) 1971-72; PhD (City)1974. Aston University: Lecturer 1974; Senior Lecturer 1988; Reader 1995; Personal Chair in Optometry 1998. Fellowship, American Academy of Optometry (FAAO)1990. Retired Aston University, August 2011; continue in 0.28 FTE position.
See: http://www.aston.ac.uk/lhs/staff/az-index/gilmartb/

Publications and Grants

• 150 publications,including five book Chapters and two edited books principally in the areas of near vision function, myopia development, mechanisms of accommodation and ocular biometry. 130 presentations with published Abstracts at Conferences in Europe, East Asia, USA, Australasia, Russia, Japan. Hong Kong and Canada.
• Grants: totalling ~£1.07M from Industry, Trusts, Charities and UK Government Bodies.

International Standing

• Editor of the academic journal of the College of Optometrists (CoO), *Ophthalmic and Physiological Optics* (*OPO*) (1987-2000); Associate Editor, February 2010 to 2014.
• Regular reviewer for all the major vision research journals and assessor for projects submitted to Canadian (NSERC), Australian (ARC), New Zealand (AMRC) and Hong Kong funding bodies.
• Research collaboration with laboratories in USA, Hong Kong, Japan, Australia and Russia.
• Exchange Fellowships with Japan and Russia (Royal Society) and Australia (Queensland University of Technology).
• Member of Optometric Advisory Boards: Sweden (The Karolinska Institute) and Hong Kong Polytechnic University (International Advisory Board, 2009-2012 and MSc in Optometry, 2011).
• European Academy of Optometry & Optics (Keynote lecture on Myopia, Copenhagen, 2010)

National Standing & External Appointments

• Assessor for project grant proposals to UK funding bodies: MRC, EPSRC, BBSRC, Welsh Office, Wellcome Trust, Leverhulme Trust, Nuffield Foundation, Mencap, National Lottery.
• External examiner for 27 PhD theses awarded by Universities of Auckland, Cardiff, Birmingham, Bradford, City, Glasgow, Hong Kong, Northumberland, QUT, Sydney, Melbourne, UMIST.
• External examiner (4-year appointments) for BSc Degree in Optometry at Universities of Manchester, Bradford, Glasgow, City and Plymouth.
• Specialist assessor (teaching) for UK HEFC 1995. GOC Panel of Visitors (educationalist category) and Chair 1997, 1999, 2001; member of GOC therapeutics working group (2003); UK QAA Panel Member for Benchmarking Optometry, 2001. UK RAE Panel, Special Advisor (Optometry) 2001; UK RAE Panel member (C12) 2005-08. Chairman of CoO Research Committee and member of Board of Trustees 2010-11. Member of CoO Research Committee 2006-present
• Keynote/Memorial Lectures: Marton (‘87); CoO Charter Lecture (‘98); Dunn (‘01); Pickwell (‘11).
• Life Fellow of CoO (2000) *‘in recognition of outstanding contribution to the College and the profession over many years*’. Founding member of the Myopia Consortium UK (MCUK) http://www.aston.ac.uk/lhs/research/health/org/myopia-consortium-uk/
• Dedicated Festschrift issue (July 2011) of *OPO* in recognition of retirement in August 2011.
• CoO Research Excellence Award. A named Award was designated in August 2011: *The Bernard Gilmartin OPO Award*; an annual Award for the best research paper published in *OPO* during the previous 5 years.
• The Association of Optometric Practitioners (AOP) ‘Lifetime Achievement Award’ received in November 2013 ‘*in recognition of outstanding lifetime contribution to the world of optics’*.

Aston University Appointments

• Convener of the Ophthalmic Research (ORG) group 1984-2010 and member 2010 to present. http://www1.aston.ac.uk/lhs/research/health/org/
• Internal supervisor for 21 PhD degrees; associate external supervisor for 4 PhD degrees.
• School of Life and Health Sciences (LHS) appointments: Director of Research for LHS 2000-‘06; Senate professorial representative; Chairman of Research Committee, member of LHS Management Committee, LHS Human Science Ethics Committee and LHS Board.
• Awarded the Chancellor’s Medal for *‘outstanding and sustained contributions to Aston University’* in July 2009.
• The *Bernard Gilmartin Optometry Scholarship Award*: established by Aston University in 2012. The annual award is to contribute to travel costs for research presentations at International Conferences by Aston University undergraduate, postgraduate and postdoctoral students.

PRÉCIS

The Précis outlines how the seven contiguous areas of research that comprise the submission evolved from my primary interest in juvenile-onset myopia. The outline refers to representative examples of work listed in the main body of the submission (Sections A to G) and to selected items of pertinent research literature.

Early revelations

The finding at 11 years-of-age that I had become 'short-sighted' was truly disconcerting and, given the apparent absence of the condition in family members or fellow pupils, prompted many hours spent in the local Manchester libraries to discover first, why I should be so afflicted, secondly, whether it would get progressively worse and thirdly whether there was any treatment available. Some solace was gleaned from '*Better Sight Without Glasses'* Benjamin's 1943 abridged version [1] of W.H. Bate's original 1920's book that advocated an unorthodox naturopathic approach to a variety of eye conditions including myopia; it transpired that some 35 years later I published a review of non-conventional methods to control myopia which addressed several of Bate's notions [C14 p20].

Academic foundations

A more comprehensive insight into the science of ametropia presented itself when I had the opportunity to join the Ophthalmic Optics BSc (Hons) degree course at City University, London in 1965. The publication of a paper based on a final year degree project [G25 p31] generated an interest in research and, in the absence of available research projects in the area of myopia, I undertook a PhD in experimental psychology at City University, London in 1969. The PhD was combined with a 1-year lectureship at City following which a 2-year period was spent in general optometric practice and then a lectureship was secured in 1974 at Aston University. The training in experimental design incorporated in the PhD programme was applied to work at Aston on various aspects of visual ergonomics and clinical instrumentation [G10-G18 p30] but interest in myopia was maintained by undergraduate teaching responsibilities in visual optics, visual perception and ophthalmic drugs. The latter required assimilation of the pharmacology and physiology of the Autonomic Nervous System (ANS) and its innervation of ciliary smooth muscle. The task was germane as, at the time (and substantiated in subsequent reviews [2, 3]) evidence from form/image-deprivation experiments on animals and epidemiological analyses indicated that the aetiology of juvenile-onset myopia was likely to be an amalgam of genetic and environmental factors that included sustained accommodation for near vision especially when coupled with high levels of cognitive demand.

Phases of research activity

Based on the premise that the inherent nature of ANS control is to acheive a balanced integration of central and peripheral processes (i.e. homeostasis) a research hypothesis was adopted that linked the aetiology of juvenile-onset myopia to a dysfunction of ANS control of sustained near vision responses. The supposition was that myopia may result from abnormal adaptation to sustained near vision as a consequence of disequilibrium of parasympathetic:sympathetic dual control of ciliary smooth muscle [C4 p19]. The hypothesis generated work in three areas of research: measurement and properties of closed- and open-loop near responses (Section A); adaptation to sustained near vision (Section B); autonomic innervation and adaptation to sustained near vision (Section C); integration of these three areas represented the first phase of research activity in myopia and near work [4, B12 p16, C18 p20]. Work in Section C may be relevant to contemporary reports on the efficacy of low-doses of topical atropine [5] in myopia control. Although atropine appears to act via a retinal/scleral route, it has been suggested that lower dosages act at more anterior sites to produce a more modulated adaptive response than occurs with higher dosages [5].

The second phase spanned the turn of the Century and was prompted by the impact of digital technology on ophthalmic instrumentation and imaging, the global recognition of the burgeoning prevalence of myopia in the adolescent population (particularly in the industrialised societies of East Asia) and the associated drive to develop clinical methods to inhibit myopia progression. The second phase thus comprised three areas of activity: ocular biometry (Section D); epidemiology (Section E); contact lenses (Section F); a fourth area encompasses several ancillary topics (Section G) which evolved over both phases. Work in the second phase is apposite to current optical methods for myopia control. Animal studies have provided evidence that contact optical devices that reduce the degree of relative peripheral hypermetropia while maintaining clear central vision [6] or present simultaneous dual focus [7] may be utilised to inhibit myopia progression in humans; the most promising of which, to date, appears to be orthokeratology [F10 p28]. A consensus has yet to emerge on the aetiological significance of peripheral refraction in human myopia [8] but its structural correlate, retinal shape, has been examined in emmetropia and myopia with reference to MRI of the posterior vitreous chamber [D10, p23,].

Taxonomy of myopia

In terms of age-of-onset, the submission concerns chiefly juvenile-onset myopia which is generally considered to have an onset between the ages of 9 and 11 years-of-age with stabilization between 15 and 18 years-of-age at around 3 to 4 dioptres; this category currently affects approximately 29% of children in the West Midlands, England [E7 p25]. Late

(or adult)-onset myopia [A16 p11] has an onset between 15 and 18 years-of-age and rarely reaches levels in excess of 2 dioptres; this category constitutes around 15% of all presenting myopia. The systemic ramifications of early-onset high myopia have also been examined in a relatively small population of children [E1 p25]. Inter-eye comparisons have been used in anisomyopia (i.e. > I dioptre difference in spherical error) to better differentiate structural change in myopia [B16 p16, D4 p23]. It has been evident that the later the onset of myopia, the lower the mean and variance of its dioptric distribution, a feature which is likely to reflect a diminishing contribution of genes to the gene: environment interaction that characterises myopia in general [3, 10-12]. Of particular interest therefore was to ascertain whether individuals with late-onset myopia were relatively more susceptible to accommodative/oculomotor dysfunction following sustained near tasks [e.g. A26 p13; B1 p15, B4, B5, B9, B11 p16; C17, C23 p20]. Work is also presented on what are generally termed the anomalous myopias, that is myopia that presents as a negative dioptric change but without immediate evidence of the well-established corollary of a correlated increase in axial length. Pseudo-myopic changes following sustained near vision are depicted as nearwork-induced transient myopia (NITM) and have been examined in children [B15 p16] and adults [B14, B16 p16, C25 p20]. Also evaluated is the myopic shift of approximately 0.75 dioptres that occurs in around 20% of individuals during the incipient phase of presbyopia (termed late-adult-onset myopia) [G6 p29]. Empty-field myopia (i.e. tonic accommodation [A29 p13]) and instrument myopia [A34 p13] also figure in the submission, the former having been utilised as a measure of accommodative adaptation [A31 p13].

Reflection

It is approaching 60 years since I first pondered over the aetiology, prevalence and treatment of my myopia and there is a still a need to understand fully why the homeostatic mechanisms regulating normal ocular growth between 6 and 15 years of age should fail and as a consequence produce myopia in a such high proportion of children [9, 10]. Myopia worldwide now affects around of 75% and 20% of East Asian and White individuals, respectively, aged between 15 and 18 years-of-age [E8, p25]. Once developed, myopia is a condition that will invariably extend over at least six decades, engender substantial economic burden and carry a significantly increased risk of ocular pathology even for moderate levels [11].

The scale and complexity of the gene-environment interaction in myopia is evident from the amalgam of factors that contribute to its onset and development [12] : intense urbanization and its effect on time spent outdoors [3, 13], education that imposes high levels of visual and cognitive demand [3] and a predisposing polygenetic profile [12]**.** Understanding

fully the bases for optical [11, 14] and pharmaceutical methods [15] of myopia control are likely to be equally complex but clinical trials will benefit from the high predictive power for future myopic error of a relatively low hyperopic mean spherical equivalent error in the young eye (e.g. <+0.75 dioptres at 6 years-of-age) [16]. This submission embodies contributions to the clinical and academic debate on the nature of myopia and its treatment; it is hoped that their translation to clinical practice will go some way to reassuring the perplexed enquiring mind of an 11-year-old with incipient myopia.

References

1. *Benjamin H. Bates, W. H. Better Eyesight Without Glasses. 1st Edn. Holt; New York (1943).*
2. *Wildsoet CF. Active emmetropization-evidence for its existence and ramifications for clinical practice. Ophthal Physiol Opt. 1997; 17:279-290.*
3. *Morgan I, Rose K. How genetic is school myopia? Prog Retin Eye Res. 2005;24:1-38.*
4. *Rosenfield M, Gilmartin B (Eds). Myopia and Nearwork Butterworth Heinemann:London, 1998;*
5. *Chia A, Chua WH, Wen L, Fong A, Goon YY, Tan D. Atropine for the treatment of childhood myopia: changes after stopping atropine 0.01%, 0.1% and 0.5%. Am J Ophthalmol. 2014;157:451–457.*
6. *Smith EL III. Prentice Award lecture 2010: A case for peripheral optical treatment strategies for myopia. Optom Vis Sci. 2011; 88:1029-1044.*
7. *McFadden SA, Tse DY, Bowrey HE, Leotta AJ, Lam CS, Wildsoet CF, To CH.. Integration of defocus by dual power Fresnel lenses inhibits myopia in the mammalian eye. Invest Ophthalmol Vis Sci. 2014;55:908–917.*
8. *Smith EL III, Campbell MCW, Irving EL. Point-counterpoint. Does peripheral retinal input explain the promising myopia control effects of corneal reshaping therapy (CRT or ortho-K) & multifocal soft contact lenses? Ophthal Physiol Opt. 2013;33:379–384.*
9. *Wallman J, Winawer J. Homeostasis of eye growth and the question of myopia. Neuron. 2004; 43:447-468.*
10. *Flitcroft DI. Is myopia a failure of homeostasis? Exp Eye Res. 2013;114: 16-24.*
11. *Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. Prog Ret Eye Res. 2012; 31:622-660.*
12. *Goldschmidt E, Jacobsen N. Genetic and environmental effects on myopia development and progression. Eye 2014;28:126–133.*
13. *Guggenheim JA, Northstone K, McMahon G, Ness AR, Deere K, Mattocks C, St Pourcain B, Williams C. Time outdoors and physical activity as predictors of incident myopia in childhood: a prospective cohort study. Invest Ophthalmol Vis Sci. 2012;53:2856–2865.*
14. *Hung GK, Ciuffreda KJ. Incremental retinal-defocus theory of myopia development - schematic analysis and computer simulation. Comp Biol Med. 2007;19: 930-946.*
15. *Ganesan P, Wildsoet CF. Pharmaceutical intervention for myopia control. Exp Rev Ophthalmol. 2010; 5:759-787.*
16. *Zadnik K, Sinnott LT, Cotter SA, Jones-Jordan LA, Kleinstein R, Manny RE, Twelker JD, Mutti DO. Prediction of juvenile-onset myopia. JAMA Ophthalmol. 2015;133::683-689.*

ACKNOWLEGEMENTS: Sincere thanks to all my collaborators, co-authors, academic friends and colleagues, funding bodies and a legion of volunteer experimental subjects.

DEDICATION: To my wife Stella Margaret

PUBLICATIONS

Published work is divided into seven Sections (A to G). Each Section includes a synopsis of the research area (with reference to selected items of pertinent literature), a list of associated publications and, to give a general indication of the relevance of publications to contemporary research literature, examples of recent citations (i.e. 4 citations that have appeared within the previous 3 years). Sections A to G are presented as separate but contiguous areas of research and publications within each Section (and subsections) are therefore listed in chronological order.

Attribution

An appraisal of my contribution to each item of published work is made with reference to six stages that encompass the progression to publication. The majority of publications have been generated by work where I have had a supervisory role and as a general policy first and corresponding authorship were assigned to postgraduate and postdoctoral students under my supervision.

A: Original concept and hypothesis A1: Primary; A2: Collaborative; A3: Intermediary

B: Acquisition, collation and quantitative analysis of the data B1: Primary; B2: Collaborative; B3: Intermediary

C: Interpretation and synthesis of the data C1: Primary; C2: Collaborative; C3: Intermediary

D: Drafting and critical revision of the manuscript for intellectual and scholastic content D1: Primary; D2: Collaborative; D3: Intermediary

E: Supervisory status E1: Principal, PhD/Post Doctoral project; E2: Associate, PhD/Post Doctoral project; E7: Not applicable

F: Research Funding Award Status F1: Principal; F2: Associate; F3: Not applicable

Citation Analyses

Total publication outputs (Sections A to G) = 145 (including book Chapters and Conference Proceedings). *Web of Science* (*WoS*) accessed 30/07/15; citation analysis based on 125 JCR-identified publications (articles only): citations (excluding self-) = 2188; h-index = 29; Citations >29 are indicated in bold adjacent to respective publications. Citing articles (excluding self-) = 1330. Average citations per item = 19.86.

SECTION A

Measurement & Properties of Closed- and Open-loop Near Vision Responses

i) Instrumentation

- ***Synopsis***

A primary task in the early 1980s was to develop instrumention that could measure components of the near vision response simultaneously and with minimal intervention. Early work used the He-Ne laser Badal optometer to measure subjectively tonic accommodation in empty-field conditions [A1] but was less suited to measurements in natural visual environments. The open-field objective binocular IR Canon Auto Ref R-1 autorefractor, launched in 1981 and evaluated clinically in 1984 [1], proved ideal for closed- and open-loop measurements of static accommodation in the laboratory and, following modification [A2], an effective facility for measuring accommodative microfluctuations.

The Auto Ref R-1 ceased production in the mid-90s and a device with similar open-view ergonomic design but different mode of operation, the Shin-Nippon SRW 5000, was introduced and thereafter followed by the S-N NVision-K/Grand Seiko WR 5100K and the portable Grand Seiko FR 5000. The standard operation of these devices were evaluated [A3, A6] and modifications made that allowed continuous [A4, A9] and simultaneous [A8] measurements of accommodative microfluctuations and pupil size.

Although photorefraction and binocular Badal optometers have also been evaluated and applied experimentally [A5, A7, A10; C19, C21 p20] the open-view desk-top autorefractors cited above feature in this submission and have been widely recognised by many laboratories as providing accessible and accurate binocular measurements of closed- and open-loop accommodative responses and pupil size (publications have collectively received, to date, over 300 citations).

Recent closed-field models [Grand Seiko AutoRef/Keratometer WAM-550 (2010) and GR-3100K/2100 (2013)] now incorporate, as standard, measurement of pupil size and repeated (5Hz sampling frequency) measurements of accommodation.

1. *McBrien NA, Millodot M. Clinical evaluation of the Canon Autoref R-1. Am J Optom Physiol Opt. 1985; 62:782-792.*

Publications

A1. Hogan RE & Gilmartin B. The choice of laser speckle exposure duration in the measurement of tonic accommodation. *Ophthal Physiol Opt.* 1984; 4:365-368. [A1, B2, C1, D1, E1, F1]

A2. Winn B, Pugh JR, Gilmartin B & Owens H. The effect of pupil size on static and dynamic measurements of accommodation using an infra-red optometer. *Ophthal Physiol Opt.* 1989; 9:277-283. [A2, B2, C2, D2, E2, F3] ***WoS* Citations = 32**

A3. Mallen EAH, Wolffsohn JS, Gilmartin B & Tsujimura SI. Clinical evaluation of the Shin-Nippon SRW 5000 autorefractor in adults. *Ophthal Physiol Opt.* 2001; 21:101-107. [A2, B2, C3, D2, E1, F1] ***WoS* Citations = 116**

A4. Wolffsohn JS, Gilmartin B, Mallen EAH & Tsujimura SI. Continuous recording of accommodation and pupil size using the Shin-Nippon SRW 5000 autorefractor. *Ophthal Physiol Opt.* 2001; 21:108-113. [A2, B2, C2, D2, E1, F1] ***WoS* Citations = 52**

A5. Wolffsohn JS, Hunt OA & Gilmartin B. Continuous measurement of accommodation in human factor applications. *Ophthal Physiol Opt.* 2002; 22:380-384. [A2, B3, C3, D2, E2] ***WoS* Citations = 33**

A6. Davies LN, Mallen EAH, Wolffsohn JS & Gilmartin B. Clinical evaluation of the Shin-Nippon NVision-K 5001/Grand Seiko WR 5100K autorefractor. *Optom Vis Sci.* 2003; 80:320-324. [A2, B3, C3, D2, E2, F2] ***WoS* Citations = 74**

A7. Hunt OA, Wolffsohn JS & Gilmartin B. Evaluation of the measurement of refractive error by the *PowerRefractor* a remote, continuous and binocular measurement system of oculomotor function. *Brit J Ophthalmol.* 2003; 87:1504-1508. [A3, B3, C3, D2, E2, F3] ***WoS* Citations = 40**

A8. Wolffsohn JS, O'Donnell C, Charman WN & Gilmartin B. Simultaneous continuous recording of accommodation and pupil size using the modified Shin-Nippon SRW-5000 autorefractor. *Ophthal Physiol Opt.* 2004; 24:142-147. [A2, B3, C3, D2, E3, F3]

A9. Wolffsohn JS, Ukai K & Gilmartin B. Dynamic measurement of accommodation and pupil responses using the portable Grand Seiko FR-5000 autorefractor. *Optom Vis Sci.* 2006; 83:306-310. [A2, B3, C2, D2, E3, F3]

A10. Wolffsohn JS, Gilmartin B, Hunt OA, & Edgar GK. Using photoretinoscopy to measure the binocular oculomotor response to monocular virtual image displays.pp 235-242 Vision in Vehicles - IX. 2012 North-Holland; Gale, AG (ed). [A3, B3, C3, D2, E2, F3]

- ***Examples of recent citations***

A2: Chakraborty R, Read SA, Collins MJ. Hyperopic defocus and diurnal changes in human choroid and axial length. Optom Vis Sci. 2013; 90:1187-1198.

A5 & A7: Zetterberg C, Richter HO, Forsman M. Temporal co-variation between eye lens accommodation and trapezius muscle activity during a dynamic near-far visual task. PLoS ONE. 2015; 10:e0126578.

A8: Ramasubramanian V, Glasser A. Can ultrasound biomicroscopy be used to predict accommodation accurately? J Refract Surg. 2015; 30:266-U155

A9: Gramatikov B, Irsch K, Guyton D. Optimal timing of retinal scanning during dark adaptation in the presence of fixation on a target: the role of pupil size dynamics. J. Biomed Opt. 2014; 19: 106014.

ii) Closed-loop Responses

- ***Synopsis***

The Canon Auto Ref R-1 and its modifications [A2] were the basis for a series of original findings on properties of closed-loop responses: stimulus eccentricity [A11, A12], the effect of

concurrent mental effort [A15, A16], pupil responses to blur-only stimulation [A18] and microfluctuations of accommodation [A17]. Investigations of microfluctuations were especially productive and resulted in reports on the frequency characteristics of microfluctuations for central and peripheral zones of the crystalline lens [A13], the modulation of steady-state accommodation by arterial pulse [A14], the influence of target luminance [A19] and the interaction between pupil size and microfluctuations during sustained near vision [A20, A21].

Later work, in collaboration with a Japanese research group, was instigated by the prospective marketing of 3-dimensional digital displays (e.g. domestic televisions) and investigated dynamic responses of accommodation to conflicting defocus- and convergence-driven stimuli presented by stereoscopic image displays [A22, A23]. A novel finding was that individual differences in responses to stereoscopic displays are influenced by the convergence accommodation:convergence ratio (CA/C) [A24].

Publications

A11. Bullimore MA & Gilmartin B. Retinal eccentricity and the accommodative response. *Am J Optom Physiol Opt.* 1987; 64:644-645. [A2, B2, C2, D2, E1, F1]

A12. Bullimore MA & Gilmartin B. The influence of retinal area stimulated on the accommodative response. In: *Advances in Diagnostic Visual Optics* (Fiorentini A, Guyton DL & Siegel IM, editors), Springer-Verlag, Berlin 1987; pp.181-185. [A2, B2, C2, D2, E1, F1]

A13. Winn B, Pugh JR, Gilmartin B & Owens H. The frequency characteristics of accommodative microfluctuations for central and peripheral zones of the crystalline lens. *Vision Res.* 1990; 30:1093-1099. [A2, B3, C2, D2, E2, F2]

A14. Winn B, Pugh JR, Gilmartin B & Owens H. Arterial pulse modulates steady-state accommodation. *Current Eye Res.*1990; 9:971-975. [A2, B3, C2, D2, E2, F3] ***WoS* Citations = 40**

A15. Winn B, Gilmartin B, Mortimer LC & Edwards NR. The effect of mental effort on open- and closed-loop accommodation. *Ophthal Physiol Opt.*1991; 11:335-339. [A2, B3, C2, D2, E1, F1]

A16. Bullimore MA, Gilmartin B & Royston J. Steady-state accommodation and ocular biometry in late-onset myopia. *Documenta Ophthalmol.* 1992; 80:143-155. [A1, B3, C2, D2, E1, F1] ***WoS* Citations = 52**

A17. Winn B & Gilmartin B. Current perspectives on accommodative microfluctuations. *Ophthal Physiol Opt.* 1992; 12:252-256. [D2] ***WoS* Citations = 34**

A18. Phillips NJ, Winn B & Gilmartin B. Absence of pupil response to blur-driven accommodation. *Vision Res.* 1992; 32:1775-1779. [A1, B2, C2, D2, E1, F1]

A19. Gray LS, Winn B & Gilmartin B. Effect of target luminance on microfluctuations of accommodation. *Ophthal Physiol Opt.* 1993; 13:258-265. [A2, B3, C2, D2, E2, F3] ***WoS* Citations = 34**

A20. Gray LS, Winn B & Gilmartin B. Accommodative microfluctuations and pupil diameter. *Vision Res.* 1993; 33:2083-2090. [A2, B3, C2, D2, E2, F3] ***WoS* Citations = 43**

A21. Gray LS, Gilmartin B & Winn B. Accommodation microfluctuations and pupil size during sustained viewing of visual display terminals. *Ophthal Physiol Opt.* 2000; 20:5-10. [A2, B3, C2, D2, E2, F3]

A22. Okada Y, Ukai K, Wolffsohn JS, Gilmartin B, Iijima A & Bando T. Target spatial frequency determines the response to conflicting defocus- and convergence-driven accommodative stimuli. *Vision Res.* 2006; 46:475-484. [A3, B3, C2, D1, E3, F3] ***WoS* Citations = 35**

A23. Torri M, Okada Y, Ukai K, Wolffsohn JS, & Gilmartin B. Dynamic measurement of accommodation while viewing stereoscopic images. *J Mod Optics* 2008; 55:557-567. [A3, B3, C2, D1, E3, F3]

A24. Fukushima T, Torii M, Ukai K, Wolffsohn JS & Gilmartin B. The relationship between CA/C ratio and individual differences in dynamic accommodative responses while viewing stereoscopic images. *J Vision* 2009: 21:1-13. [A3, B3, C2, D1, E3, F3]

- ***Examples of recent citations***

A14: Gabriel C, Klaproth OK, Titke C, Baumeister M, Buehren J, Kohnen T. Repeatability of topographic and aberrometric measurements at different accommodative states using a combined topographer and open-view aberrometer. J Cat Refract Surg. 2015; 41:806-811.

A17: Jeng WD, Ouyang Y, Huang TW, Duann JR, Chiou JC, Tang YS, Ou-Yang M. Research of accommodative microfluctuations caused by visual fatigue based on liquid crystal and laser displays. Applied Optics 2014; 53:H76-H84.

A18: Binda P, Murray SO. Spatial attention increases the pupillary response to light changes. J Vision 2015; 15:Issue 2 Article 1.

A24: Zeri F, Livi S. Visual discomfort while watching stereoscopic three-dimensional movies at the cinema. Ophthal Physiol Opt. 2015; 35:271-282.

iii)Open-Loop Responses

- ***Synopsis***

My interest in tonic accommodation [the intermediate resting position of accommodation (~1 dioptre) that occurs under open-loop conditions] developed in the early 1980s. Measurement with an open-view optometer [A25] facilitated a range of investigations and various properties of tonic accommodation were reviewed [A29, A31] and evaluated [A28, A32] and its corollary, tonic vergence [A30] was shown to be influenced by perceived proximity. Early evidence that tonic accommodation varies with refractive error [A26] was equivocal and likely to be affected by the method of measurement [A33].

The work on instrumentation, closed-loop and open-loop reponses and the influential publication by Fisher *et al.* [1] on tonic accommodation, accommodative hystereses and refractive error had, by the mid-1980s, laid the foundations to explore further the nature of adaptation to sustained near vision (Section B) and its connection with autonomic innervation (Section C). A novel idea, referred to further in Section B and utilised particularly in Section C, was that, being a stimulus-free measure, the temporal properties of tonic accommodation i.e. the regression of within-task closed-loop accommodation to a

post-task open-loop tonic resting position, might provide a useful experimental tool to measure within-task adaptation to sustained near vision responses.

1. Fisher SK, Ciuffreda KJ, Levine S. Tonic accommodation, accommodative hysteresis and refractive error. Am J Optom Physiol Opt. 1987; 64:799-809.

Publications

A25. Bullimore MA, Gilmartin B & Hogan RE. Objective and subjective measurement of tonic accommodation. *Ophthal Physiol Opt.* 1986; 6:57-62. [A1, B2, C2, D1, E1, F1]

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A27. Bullimore MA, Boyd T, Mather HE & Gilmartin B. Near retinoscopy and refractive error. *Clin Exp Optom.* 1988; 71:114-118. [A2, B3, C3, D3, E1, F1]

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SECTION B

Adaptation to Sustained Near Vision

- ***Synopsis***

Adaptation to a sustained near task is likely to be a complex aggregate of optical, non-optical, cognitive and visual ergonomic factors [1, B10]. Initially, five studies examined adaptation to near vision with reference to simultaneous closed-loop measures of accommodation and vergence [B1, B2, B4-B6]. Two temporal components are evident in the aggregate blur-driven within-task accommodative response: a fast blur-driven component (FBAR) which acts rapidly (typically within 1 second) to reduce retinal defocus and initiate a slow blur-driven component (SBAR) [B12, C10 p20]. When near vision is sustained (i.e. generally of duration greater than 30 seconds) FBAR dissipates to allow SBAR to maintain the aggregate accommodative response relatively constant and of sufficient magnitude to optimise the lag of accommodation.

Given that accommodative adaptation reflects the maintained output of SBAR it was proposed that individuals deficient in SBAR will exhibit larger lags of accommodation, persistent retinal defocus and hence susceptibility to myopia [B12]. Further, as FBAR and SBAR receive inputs from both acccommodative-convergence and convergent-accommodation cross-links [B6] it was predicted, and demonstrated for both early- and late-onset myopes [B2], that a deficiency in SBAR would preferentially channel the cross-links to the FBAR and hence, owing to its lack of an adaptive facility, enhance accommodative lag an elevated AC/A ratio and esophoria at near. In contrast and consistent with the proposal that a deficient SBAR may have aetiological significance neither early- nor late-onset myopes could be differentiated from emmetropes with regard to CA/C ratios [B4]. Of relevance is that a slowing of myopia progession by reducing accommodative effort at near with progessive addition spectacle lenses is statistically, but not clinically, significant in myopic children with high accommodative lag [2]. Further, an elevated AC/A ratio at 8 years-of-age is a significant predictor for future onset of juvenile-onset myopia [3].

When an individual views a distant target under closed-loop conditions immediately following completion of a sustained near-task the relatively prolonged decay of SBAR may produce an excessive accommodative response [i.e. a lead of accommodation termed nearwork-induced transient myopia (NITM)]. It has been proposed [4] that the relatively small amounts of retinal defocus produced (typically around 0.2 of a dioptre sustained for over 60 seconds and repeatable) may ultimately stimulate axial elongation. Several investigations were, in due course, carried out on NITM [B14-B16] and the proposal that the

susceptibility of early-and late-onset myopes to NITM may be attributable to impaired sympathetic innervation in myopia [5] was examined in a subsequent study [C25 p20]. In terms of adaptation and myopia development NITM is an intriguing phenomenon [6, 7] despite a very recent 3-year longitudinal study on a large sample of Chinese subjects aged 6 to 17 years-of-age that could not associate NITM with the progression of myopic error [8].

The measurement of closed-loop within-task adaptation using regression of accommodation to a post-task open-loop tonic resting position was introduced in Section A iii) p12. Regressons have been shown to be repeatable [B11] and independent of the post-task open-loop condition [B8]. Experiments on binocular status [B3, B7] and within-task dioptric demand [B9] indicate that reduced within-task accommodative adaptation occurs in late-onset myopia compared with emmetropia. Importantly, the classification of non-adaptors and adaptors based on the attenuation of post-task regression to the tonic position was shown to correlate with the degree of within-task accommodative lag [B13], that is, a lack of post-task attenuation produced a greater level of accommodative lag.

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SECTION C

Autonomic Innervation and Adaptation to Sustained Near Vision

- ***Synopsis***

By the early to mid-1980s the concurrent series of investigations on objective open-view methods of measurement [Section A i) p9], tonic accommodation [Section A iii) p12] and adaptation (Section B p14) provided the foundations to test the research hypothesis that linked the aetiology of juvenile-onset myopia to a dysfunction of ANS control of sustained near vision responses. Based on the premise that the inherent nature of ANS control is to provide a balanced integration of central and peripheral processes (i.e. homeostasis) the supposition was that myopia may result from abnormal adaptation to sustained near vision as a consequence of disequilibrium of parasympathetic:sympathetic dual control of ciliary smooth muscle [C4].

A review of literature on anatomical, physiological and pharmacological aspects of dual innervation of ciliary smooth muscle provided evidence that, in contrast to parasympathetic innervation, sympathetic innervation was inhibitory in nature. In addition, bio-engineering models had postulated a synergistic accommodation control system whereby dual innervation operated in normal visual environments [C4].

An opportunity to investigate dual innervation in humans *in vivo* was presented following the availability in the early 1980s of a topical preparation of timolol maleate for the treatment of open-angle glaucoma. Timolol's principal pharmacological action is to act on the sympathetic nervous system by the non-selective blocking of beta-1 and beta-2 adrenoceptors. Significant myopic shifts in the tonic resting position of accommodation with timolol (independent of its ocular hypotensive effect and against a saline control) demonstrated for the first time *in vivo* the inhibitory nature beta-receptor activity in ciliary smooth muscle [C1]. Confirmation of the inhibitory action was provided by the significant hyperopic shifts in tonic accommodation produced by the non-selective beta-adrenoceptor agonist isoprenaline [C3].

The differential response of tonic accommodation to beta-adrenoceptor antagonist and agonist action demonstrated that the magnitude of beta-adrenoceptor inhibition was positively correlated with the magniture of prevailing background paraympathetic activity [C1, C3]. The observation led to the key study in 1987 which measured post-task regression of tonic accommodation to pre-task levels following closed-loop distance and near vision tasks and reported for the first time that sustained near-vision augments inhibitory sympathetic innervation of ciliary smooth muscle [C6].

A series of studies followed on the effects of sympathetic innervation on oculomotor function [C7, C8] cognition [C5, C9] and temporal aspects of accommmodative adaptation [C10] and presented data that were consistent with the inhibitory nature of sympathetic innervation of ciliary smooth muscle. Ancillary investigations considered the effect of topical beta-adrenoceptor antagonists on microfluctuations of accommodation [C12, C16] and general autonomic correlates of accommodation and cardiovascular function [C24, C26].

The topical selective (for beta-1 adrenoceptors) beta- antagonist betaxolol hydrochloride subsequently became available and replaced saline as the control agent for the non-selective action of timolol. Using a previous protocol [C6] work was thus able to demonstrate that inhibitory sympathetic innervation of ciliary smooth muscle is mediated by beta-2 adrenoceptors [C17, C21-C23] and that the inhibitory effect was equivalent for individuals with emmetropia, early-onset myopia and late-onset myopia [C17]. Further, sympathetic inhibition was shown to be present in only one third of participating subjects [C22] irrespective of whether they were early-onset myopes, late-onset myopes or emmetropes [C23]. A subsequent study on near-work induced transient myopia (NITM) found again that one in three subjects with myopia exhibited a significant increase in post-task duration of decay of NITM following topical timolol (with betaxolol used as a control) [C25].

Observations in Section C may be relevant to contemporary reports on the efficacy of low-doses of topical atropine (a parasympathetic antagonist for muscarinic receptors on ciliary smooth muscle) in myopia control in Chinese children [1]. Atropine appears to upregulate or downregulate muscarinic receptors in the retina and sclera which then either directly or indirectly alter the sclera matrix and thus the degree of scleral creep and ocular elongation [1, 2]. It has, however, also been suggested that lower dosages of atropine act at more anterior sites to produce a more modulated adaptive response than occurs with higher dosages [1]. Further, recent work using surgical [3] and pharmaceutical [4] interventions in avian experimental myopia may offer scope for future experimental paradigms. In the latter, chicks exposed to illumination conditions that selectively stimulate colour and luminance emmetropization mechanisms showed opposing growth and refractive effects and choroidal compensation in response to atropine and timolol. It was suggested that a precise balancing mechanism between the parasympathetic:sympathetic system and the visual environment may operate to achieve emmetropization [4].

As expressed by Flitcroft [5], compared to other biological traits, the nature, scale and complexity of gene-environment interactions in refractive development require optimum homeostatic control. It may be, therefore, that myopia will result when homeostatic control of refractive state by the ANS is challenged by an amalgam of factors known to contribute

to its onset and development: intense urbanization and its effect on time spent outdoors [6], educational conditions that impose high levels of visual and cognitive demand and a predisposing polygenetic profile [7]. It is, however, presently unclear how the modulation of adaptative processes by sympathetic innervation of ciliary muscle demonstrated in Section C contributes to homeostatic control of growth in the posteror segment [C18, C20].

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C26. Davies LN, Wolffsohn JS & Gilmartin B. Autonomic correlates of ocular accommodation and cardiovascular function *Ophthal Physiol Opt.* 2009; 29:427-435. [A3, B3, C3, D2, E2, F3]

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SECTION D

Ocular Biometry

- ***Synopsis***

The second phase of research activity spanned the turn of the Century and was prompted by the impact of digital technology on ophthalmic instrumentation and imaging, the global recognition of the burgeoning prevalence of myopia in the adolescent population (particularly in the industrialised societies of East Asia) and the associated drive to develop clinical methods to inhibit the progression of myopia [D3]. The second phase thus comprised three further areas of activity: ocular biometry (Section D); epidemiology (Section E p24); contact lenses (Section F p26); a fourth area encompasses several ancillary topics (Section G p28) which evolved over both phases.

Work in the second phase has been apposite to current methods and strategies for myopia control. Animal studies have provided evidence that contact optical devices that reduce the degree of relative peripheral hypermetropia while maintaining clear central vision [1] or present simultaneous dual focus [2] may be utilised to inhibit myopia progression in humans; the most promising of which appears to be orthokeratology [F10 p28]. A key development early in 2001 was the application of non-contact partial coherent interferometry to ocular biometry (i.e. the Zeiss *IOLMaster*) and our laboratory was the first to evaluate shortly thereafter its utility in providing non-contact high resolution measures of axial length [D2].

A consensus has yet to emerge on the aetiological significance of peripheral refraction in human myopia [3, 4] but its structural correlate, retinal shape [5], has been examined with reference to the ocular biometry of the posterior vitreous chamber. Initial work using the

open-field Canon autorefractor [A2 p10] used a bespoke computer program to determine retinal contour from several basic ocular biometric parameters, including peripheral refraction [D1]. By comparing contours in iso- and anisomyopic eyes of young adults the method was used to show symmetry in nasal:temporal expansion of Taiwanese-Chinese eyes but asymmetry in expansion (nasal > temporal) in white European eyes [D4].

A major contribution was the use of a 3-T MRI to generate T2-weighted images for 3-dimensional *in vivo* representation of the human eye [D5, D6]. The technique is not affected by the distortions produced by optical methods and has been used to report on ocular volume [D11] and surface area [D13, P1 p32], submit a patent application on a novel clinical method of myopia control [D7] and analyse the shape of the posterior vitreous chamber in emmetropia and non-pathological myopia [D10, P2 p32]. The latter study [D10] has presented a number of original observations concerning the nature of ocular growth e.g. prolate ellipse posterior chamber shapes are rarely found in non-pathological myopia; enhanced sphericity (compared with emmetropia) is a feature of the posterior segment in myopia and may constitute a biomechanical limitation on further axial elongation; a laterality effect was demonstrated, that is a coupling of retinal shape between RE temporal quadrants and LE nasal quadrants and *visa versa* - synchronization of quadrant retinal shapes with retinotopic projection suggests that binocular growth is coordinated by processes that operate beyond the optic chiasm [D10]. Confirmatory evidence for synchronisation has been recently obtained by comparing off-axis to on-axis measurements of axial length using an optical method (i.e. partial coherent interferometry [D14]).

To complement information on posterior segment dimensions provided by the MRI technique work has subsequently explored regional variations in ciliary body thickness [D9] and anterior scleral thickness [D12] (using optical coherent tomography) together with investigations on anterior scleral rigidity [D8, P3 p32]. Variation in the associations between ciliary body thickness, axial length and ocular volume in myopic and non-myopic eyes suggests that myopia may result from a breakdown in co-ordination between growth of the anterior and posterior segments possibly linked to imprecise neural feedback between the fovea and ciliary apparatus [D9, D12].

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3. *Charman WN, Radhakrishnan H. Peripheral refraction and the development of refractive error. Ophthal Physiol Opt. 2010; 30:321-338.*

4. *Smith III EL, Campbell MCW, Irving EL. Point-counterpoint. Does peripheral retinal input explain the promising myopia control effects of corneal reshaping therapy (CRT or ortho-K) & multifocal soft contact lenses? Ophthalmic Physiol Opt. 2013; 33:379–384.*

5. *Verkicharla PK, Mathur A, Mallen EAH, Pope JM, Atchison DA. Eye shape and retinal shape, and their relation to peripheral refraction. Ophthal Physiol Opt. 2012; 32:184-189.*

Publications

D1. Logan NS, Gilmartin B & Dunne MCM. Computation of retinal contour in anisomyopia. *Ophthal Physiol Opt.* 1995; 15:363-366. [A1, B2, C2, D2, E1, F1]

D2. Santodomingo-Rubido J, Mallen EAH, Gilmartin B & Wolffsohn JS. A new non-contact device for ocular biometry. *Brit J Ophthalmol.* 2002; 86:458-462. [A2, B3, C2, D1, E1, F1] ***WoS* Citations = 125**

D3. Gilmartin B. Myopia: precedents for research in the 21st Century. *Clin Exp Ophthalmol.* 2004; 32:305-324. [D1] ***WoS* Citations = 62**

D4. Logan NS, Gilmartin B, Wildsoet CF & Dunne MCM. Posterior retinal contour in adult human anisomyopia. *Invest Ophthal Vis Sci.* 2004; 45:2152-2162. [A2, B2, C2, D2, E2, F3] ***WoS* Citations = 80**

D5. UK Patent Application GB0426243.2 November 2004: Method and Apparatus for Imaging the Eye. Professor KD Singh, Professor B Gilmartin, Dr NS Logan. (pdf not available). [A2, B2, C2, D2, E3, F3]

D6. Singh KD, Logan NS & Gilmartin B. Three-dimensional modelling of the human eye based on magnetic resonance imaging. *Invest Ophthalmol Vis Sci.* 2006; 47:2272-2279. [A1, B3, C3, D2, E3, F3] ***WoS* Citations = 57**

D7. UK Patent Application GB1012040.0 July 2010: Apparatus and method for affecting the progression of eye refractive error. Professor Stephen Anderson and Professor Bernard Gilmartin. (pdf not available). [A1, B2, C2, D2, E3, F3]

D8. Patel H, Gilmartin B, Cubbidge R, & Logan NS. *In vivo* measurement of regional variation in anterior scleral resistance to Schiotz indentation. *Ophthal Physiol Opt.* 2011; 31:437–443. [A2, B2, C2, D2, E2, F3]

D9. Buckhurst H, Gilmartin B, Cubbidge RP, Nagra M & Logan NS. Ocular biometric correlates of ciliary muscle thickness in human myopia. *Ophthal Physiol Opt.* 2013*;* 33:294-304. [A1, B2, C2, D2, E1, F3]

D10. Gilmartin B, Nagra M & Logan NS. Shape of the posterior vitreous chamber in human emmetropia and myopia. *Invest Ophthalmol Vis Sci.* 2013; 54:7240-7251. NOTE: This paper has additional material published as a supplement. (see pdf D10S) [A1, B3, C1, D1, E1, F1]

D11. Nagra M, Gilmartin B, Logan NS. Estimation of ocular volume from axial length. *Brit J Ophthalmol.* 2014; 98:1697-1701. [A1, B2, C1, D1, E1, F1]

D12. Buckhurst H, Gilmartin B, Cubbidge RP & Logan NS. Measurement of scleral thickness in humans using anterior segment optical coherent tomography**.** *PLoSONE* 2015; 10:e0132902. [A2, B2, C2, D2, E1, F3]

D13. Nagra M, Gilmartin B, Thai NJ, Logan NS. The concordance of variations in inter-quadrant susceptibility to retinal breaks and retinal surface area. *Eye* 2015; (Under Review - Abstract). [A1, B2, C1, D1, E1, F1]

D14. Logan NS, Percy EJ, Gilmartin B. Asymmetry and laterality of posterior chamber dimensions in young adults. International Myopia Conference, Wenzou, China, September 2015. (Under Review - Abstract) [A1, B3, C2, D1, E3, F3]

- ***Examples of recent citations***

D1 & D4: Faria-Ribeiro M, Lopez-Gil N, Navarro R et al. Computing retinal contour from optical biometry. Optom Vis Sci. 2014; 91:430-436.

D3: Loh KL, Lu Q, Tan D et al. Risk factors for progressive myopia in the atropine therapy for myopia study. Am J Ophthalmol. 2015; 159:945-949.

D4, D6 & D10: Lim L, Shen CS, Tan T et al. Eye size and shape in newborn children and their relation to axial length and refraction at 3years. Ophthal Physiol Opt. 2015; 35:414-423.

D6: Beenakke JWM, Shamonin DP, Webb AG et al. Automated retinal topographic maps measured with magnetic resonance imaging. Invest Ophthalmol Vis Sci. 2015; 56:1033-1039.

SECTION E

Epidemiology

- ***Synopsis***

Initial work on epidemiology concerned high myopia in children [E1], anisometropia [E2], school screening for myopia [E3] and myopia prevalence in a UK student community [E5]. A major contribution has been the establishment of the Aston Eye Study (AES) [E7].

AES is an ongoing multiracial cross-sectional study of children selected from schools in the metropolitan Birmingham area of central England and examines how various exposures in early life influence visual development at different stages during childhood and whether there are ethnic differences in development. The effect of time outdoors and physical activity as predictors of incident myopia is currently receiving much attention [1] and is therefore of particular interest in the questionnaire used by AES. The findings to date indicate the emergence of higher levels of myopia by early adolescence in second and third generation British South Asians, compared to white European children [E7].

The Northern Ireland Childhood Errors of Refraction Study (NICER) followed the same protocol as AES for urban and rural children in Northern Ireland [E6] and has since reported on its findings [2, 3]. Current work continues with collaborators from both the AES and NICER studies (i.e. Rudnicka AR and Owen CG) on a major systematic review of global variations and time trends in the prevalence of childhood myopia [E8]. Marked ethnic differences have been demonstrated in age-sex standardized estimates of myopia prevalence and among populations of the same ethnicity residing in different geographical/environmental locations. Females have a higher prevalence of myopia

compared to males from around 9 years and gender differences become more marked with age. The data confirm that an urban environment is associated with a higher risk of myopia with, in particular, significant rapid increases over time in East Asians [E8].

It is emerging however that interpretation and comparison of epidemiological data on the prevalence of myopia and associated gene-environment interactions needs to take full account of the taxonomy of myopia under examination [p6 para 2] in terms of models of refractive deveopment [4] and differences in statistical distributions of dioptric error [5].

1. *Guggenheim JA, Northstone K, McMahon G, Ness AR, Deere K, Mattocks C, St Pourcain B, Williams C. Time outdoors and physical activity as predictors of incident myopia in childhood: a prospective cohort study. Invest Ophthalmol Vis Sci. 2012; 53:2856–2865.*

2. *O'Donoghue L, McClelland JF, Logan NS et al. Refractive error and visual impairment in school children in Northern Ireland. Brit J Ophthalmol. 2010; 94:1155-1159.*

3. *O'Donoghue L, Kapetanankis VV, McClelland JF et al. Risk factors for childhood myopia: findings from the NICER study. Invest Ophthalmol Vis Sci. 2015; 56:1524-1530.*

4. *Hung GK, Ciuffreda KJ. Model of human refractive error development. Curr Eye Res. 1999; 19:41-52.*

5. *Plainis S, Charman WN. Problems in comparisons of data for the prevalence of myopia and the frequency distribution of ametropia. Ophthal Physiol Opt. 2015; 35:394-404.*

Publications

E1. Logan NS, Gilmartin B, Marr JE, Stevenson MR & Ainsworth JR. Community-based study of the association of high myopia in children with ocular and systemic disease *Optom Vis Sci.* 2004; 81:11-13. [A1, B3, C2, D2, E1, F1]

E2. Pointer JS, Gilmartin B. Clinical characteristics of unilateral myopic anisometropia in a juvenile optometric practice population. *Ophthal Physiol Opt.* 2004; 24:458-463. [A1, B3, C2, D2, E3, F3]

E3. Logan NS, Gilmartin B. School vision screening ages 5 to 16 years: the evidence-base for content, provision and efficacy *Ophthal Physiol Opt.* 2004; 24:481-492. [D2]

E4. Logan NS, Gilmartin B. Myopia: development and control in children. *Optometry in Practice* 2005; 6:149-162. [D2]

E5. Logan NS, Davies LN, Mallen EAH & Gilmartin B. Ametropia and ocular biometry in a UK University student population. *Optom Vis Sci.* 2005; 82:261-266. [A2, B3, C3, D2, E1, F1] ***WoS* Citations = 34**

E6. O'Donoghue L, Saunders KJ, McClelland JF, Logan NS, Rudnicka AR, Gilmartin B & Owen CG. Sampling and measurement methods for a study of childhood refractive error in a United Kingdom population. *Brit J Ophthalmol.* 2010; 94:1150-1154. [A2, B3, C3, D2, E3, F2]

E7. Logan NS, Shah P, Rudnicka AR, Gilmartin B & Owen CG. Childhood ethnic differences in ametropia and ocular biometry: the Aston Eye Study. *Ophthal Physiol Opt.* 2011; 31:550–558. [A1, B2, C2, D2, E2, F2]

E8. Rudnicka AR, Kapetanakis V, Wathern AK, Logan NS, Gilmartin B et al. Global variations and time trends in the prevalence of childhood myopia, a systematic review: implications for aetiology and early prevention. *Eur J Epidemiol* (Under Review- Abstract). [A2, B3, C3, D2, E3, F2]

- ***Examples of recent citations***

E1: Cheng SCK, Lam SSY, Yap MKH. Prevalence of myopia-related retinal changes among 12-18 year old Hong Kong Chinese high myopes.Ophthal Physiol Opt. 2013; 33:652-669.

E3: Hopkins S, Sampson GP, Hendicott P et al. Review of guidelines for children's vision screenings. Clin Exp Optom. 2013; 96:443-449.

E5: Williams KM, Hysi PG, Nag A et al. Age of myopia onset in a British population-based twin cohort. Ophthal Physiol Opt. 2013; 33:339-345.

E7: French AN, Morgan IG, Mitchell P et al. Risk Factors for incident myopia in Australian schoolchildren The Sydney Adolescent Vascular and Eye Study. Ophthalmology 2013; 120:2100-2108.

SECTION F

Contact Lenses

i) Conventional Contact Lenses.

- ***Synopsis***

Following reports that the wearing of soft lenses might exacerbate myopia progression and associated changes in ocular biometry [1] an 18-month longitudinal study of neophyte contact lens wearers was carried out that compared changes in refraction and biometry induced by daily wear and continuous wear of two different types of silicone hydrogel (SiH) materials [F3]. Increases in myopia, similar to those found to occur normally in young-adult non-contact lens wearers were also evident with SiH contact lens wear, the main biometric contributor to the progression of myopia being a correlated increase in axial length. A series of investigations on adverse effects of SiH lens wear followed [F5-F7] but it was apparent that the prospects for myopia control with contact lenses were limited if restricted to conventional single-vision contact lens designs [F4].

1. *Fulk GW, Cyert LA, Parker DE et al. The effect of changing from glasses to soft contact lenses on myopia progression in adolescents. Ophthal Physiol Opt 2003; 23:71–77.*

Publications

F1. Pointer JS, Gilmartin B & Larke JR. The investigation of the visual performance of the contact lens wearer. *J Brit Contact Lens Assoc.* 1980; 3:158-160. [A3, B3, C2, D2, E2, F3]

F2. Pointer JS, Gilmartin B & Larke JR. Visual performance with soft hydrophilic contact lenses. *Am J Optom Physiol Opt.* 1985; 62:694-701. [A2, B2, C2, D2, E2, F3]

F3. Santodomingo-Rubido J, Gilmartin B & Wolffsohn JS. Refractive and biometric changes with silicone hydrogel contact lenses. *Optom Vis Sci.* 2005; 82:481-489. [A2, B3, C2, D2, E2, F1]

F4. Logan NS & Gilmartin B. Contact lens correction and myopia progression. In: *Contact Lenses* (Phillips AJ & Speedwell L, editors), Butterworth Heinemann: Oxford, 2006; pp.591-600. [D2]

F5. Santodomingo-Rubido J, Wolffsohn JS & Gilmartin B. Changes in ocular physiology, tear film characteristics and symptomatology with 18 months silicone hydrogel contact lens wear. *Optom Vis Sci.* 2006; 83:73-81. [A2, B3, C2, D2, E2, F1]

F6. Santodomingo-Rubido J, Wolffsohn JS & Gilmartin B. Adverse events and discontinuations during 18 months of silicone hydrogel contact lens wear. *Eye Contact Lens.* 2007; 33:288-292. [A2, B3, C2, D2, E2, F1]

F7. Santodomingo-Rubido J, Wolffsohn JS & Gilmartin B. Conjunctival epithelial flaps with 18 months silicone hydrogel contact lens wear. *Eye Contact Lens.* 2008; 33:35-38. [A2, B3, C2, D2, E2, F1]

ii) Myopia Control with Contact Lenses (Orthokeratology)

- ***Synopsis***

Two key studies [1, 2] provided the first evidence that corneal flattening using reverse-geometry rigid contact lens wear in children (i.e. orthokeratology - OrthoK) could inhibit axial length growth and instigated the longitudinal study 'Myopia Control with Orthokeratology contact lenses in Spain' designated MCOS [F8]. MCOS was subsequently able to demonstrate for the first time, in comparison with distance single-vision spectacles, a significant reduction in axial length (the primary outcome measure) over a 2-year period in white myopic European children wearing OrthoK contact lenses [F10].

A series of associated publications investigated related aspects of adverse events and discontinuations of lens wear [F9], quality-of-life measures [F11] and short-term post-OrthoK changes in ocular biometry and refraction following termination of the MCOS clinical trial [F13]. Attention has been directed more recently to understanding better the optical basis of myopia control using OrthoK, particularly with regard to its effect on the formation of the peripheral retinal image shell [F14-F16].

1. *Cho P, Cheung SW, Edwards M. The longitudinal orthokeratology research in children (LORIC) in Hong Kong: a pilot study on refractive changes and myopic control. Current Eye Res. 2005; 30:71-80.*

2. *Walline JJ, Jones LA, Sinnott LT. Corneal reshaping and myopia progression. Br J Ophthalmol. 2009; 93:1181-1185.*

Publications

F8. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B & Gutiérrez-Ortega R. Myopia Control with Orthokeratology contact lenses in Spain (MCOS): study design and general baseline characteristics. *J Optometry* 2009; 2:215-222. [A2, B3, C2, D2, E3, F3]

F9. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B & Gutiérrez-Ortega R. Orthokeratology vs. Spectacles: adverse events and discontinuations. *Optom Vis Sci.* 2012; 89:1133-1139. [A2, B3, C2, D2, E3, F3]

F10. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B & Gutiérrez-Ortega R. Myopia control with orthokeratology contact lenses in Spain (MCOS): refractive and biometric changes. *Invest Ophthalmol Vis Sci.* 2012; 53:5060-5065. [A2, B3, C2, D1, E3, F3] ***WoS* Citations = 33**

F11. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B & Gutiérrez-Ortega R. Myopia Control with Orthokeratology contact lenses in Spain (MCOS): a comparison of vision-related quality-of-life measures between contact lenses wear and single-vision spectacle lens wear. *Eye Contact Lens* 2013; 39:153-157. [A2, B3, C2, D2, G1]

F12. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B & Gutiérrez-Ortega R. Factors preventing myopia progression with orthokeratology correction. *Optom Vis Sci.* 2013; 90:1225-1236. [A2, B3, C2, D2, E3, F3]

F13. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B & Gutiérrez-Ortéga R. Short-term changes in ocular biometry and refraction following discontinuation of long-term orthokeratology. *Eye Contact Lens* 2014; 40:84-90. [A2, B3, C2, D2, E3, F3]

F14. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B & Gutiérrez-Ortega R. The effects of entrance pupil centration and coma aberrations on myopia progression following orthokeratology. *Clin Exp Optom.* 2015; (In Press - Proofs) [A2, B3, C2, D2, E3, F3]

F15. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B & Gutiérrez-Ortéga R. Short- and long-term changes in corneal power are not correlated with axial elongation of the eye induced by orthokeratology in children. *Invest Ophthalmol Vis Sci.* 2015; (Under Review - Abstract) [A2, B3, C2, D2, E3, F3]

F16. Santodomingo-Rubido J, Villa-Collar C, Gilmartin B, Gutiérrez-Ortéga R & Susaki A. Changes in corneal aberrations and axial length induced by orthokeratology in children are not associated. *Invest Ophthalmol Vis Sci.* 2015; (Under Review - Abstract). [A2, B3, C2, D2, E3, F3]

- ***Examples of recent citations***

F9 & F10: Wen D, Huang J, Chen H et al. Efficacy and acceptability of orthokeratology for slowing myopic progression in children: A systematic review and meta-analysis. J Ophthalmol. 2015: 360806.

F10 & F12: Si JK, Tang K, Bi HS, Guo DD, Guo JG, Wang XR. Orthokeratology for myopia control: A meta-analysis. Optom Vis Sci. 2015; 92:252-257.

F10: Sun Y, Xu F, Zhang T et al. Orthokeratology to control myopia progression: A meta-analysis. PLoS ONE 2015; 10:e0124536.

F13: Felipe-Marquez G, Nombela-Palomo M, Cacho I et al. Accommodative changes produced in response to overnight orthokeratology. Graefes Arch Clin Exp Ophthalmol. 2015; 253:619-626.

SECTION G

Ancillary Topics

i) Presbyopia

- ***Synopsis***

Of the ancilliary work presented, publications on presbyopia are most directly related to myopia. Initial informal observations from clinical practice, later confirmed [G6], indicated

that a proportion of individuals (approximately 20%) with incipient presbyopia (i.e. the period immediately preceding the prescribing of a reading addition for near) exhibit a significant myopic shift in refraction, generally of the order of 0.75 dioptres. It appears likely that the shift is attributable to lenticular or extralenticular change [1, G2, G3] and possibly oculomotor adaptation [G1, G4, G5] rather than a correlated increase in axial length [2]. The characteristics of myopia onset and progression in the mature, developed eye is of special interest as recent work [3] indicates that the prevalence of myopia (≤ - 0.75 dioptres) in adult eyes of Europeans (≥ 25 and < 90 years-of-age) is 30.6%.

1. *Charman WN. The eye in focus: accommodation and presbyopia. Clin Exp Optom. 2008; 91:207-225.*

2. *Laughton DS. Optical and structural ocular changes during incipient presbyopia. Unpublished PhD Thesis. January 2015 (Principal supervisor Dr LN Davies).*

3. *Williams KM, Verhoeven VJM, Cumberland P, Bertelsen G et al. Prevalence of refractive error in Europe: the European Eye Epidemiology (E3) Consortium. Eur J Epidemiol. 2015; 30:305–315.*

Publications

G1. Winn B, Gilmartin B, Sculfor DL & Bamford JC. Vergence adaptation and senescence. *Optom Vis Sci.* 1994; 71:797-808. [A2, B3, C2, D2, E3, F3]

G2. Gilmartin B. The aetiology of presbyopia: a summary of the role of lenticular and extralenticular structures. *Ophthal Physiol Opt.* 1995; 15:431-437. [D1] ***WoS* Citations = 42**

G3. Bullimore MA & Gilmartin B. Hyperopia and presbyopia: etiology and prevalence. In *Surgery for Hyperopia and Presbyopia* (Sher NA, ed.), Williams and Wilkins: Baltimore, 1997; pp.3-10. [D2]

G4. Baker FJ & Gilmartin B. The effect of incipient presbyopia on the correspondence between accommodation and vergence. *Graefe's Arch Clin Exp Ophthalmol.* 2002; 240:488-494. [A1, B2, C1, D1, E1, F1]

G5. Baker FJ & Gilmartin B. A longitudinal study of vergence adaptation in incipient presbyopia. *Ophthal Physiol Opt.* 2003; 23:507-511. [A1, B2, C1, D1, E1, F1]

G6. Pointer JS & Gilmartin B. Patterns of refractive change in myopic subjects during the incipient phase of presbyopia: a preliminary study. *Ophthal Physiol Opt.* 2011; 31:489–493. [A1, B3, C2, D2, E3, F3]

ii) Pupil Responses to Colour

- ***Synopsis***

Studies on pupil responses and the visual pathway developed out of previous work on open-view continuous measurement of pupil and accommodation [A4 p10]. Pupil responses to colour indicated that the pupillary iso-response contour is consistent with psychophysical measurement at high stimulus contrast which suggested that the retino-cortical pathway can be investigated using pupil measurements and hence have application in clinical and fundamental research [G7]. The work progressed futher to show,

for the first time, that pupillary constriction associated with the complementary coloured afterimage (on stimulus extinction) is mediated by the magno-cellular pathway [G8]. The sensitivity of the chromatic pathway, in terms of pupillary response, was also shown to be three times larger than that of the luminance pathway [G9], a property that might have utility in clinical applications.

Publications

G7. Tsujimura SI, Wolffsohn JS & Gilmartin B. A linear chromatic mechanism drives the pupillary response. *Proc R Soc Lond* B. 2001; 268:2203-2209. [A3, B3, C2, D1, E1, F1]

G8. Tsujimura SI, Wolffsohn JS & Gilmartin B. Pupil responses associated with coloured afterimages are mediated by the magno-cellular pathway. *Vision Res.* 2003; 43:1423-1432. [A3, B3, C2, D1, E2, F1]

G9. Tsujimura SI, Wolffsohn JS & Gilmartin B. Pupil response to colour signals in cone contrast space. *Current Eye Res.* 2006; 31:401-408. [A3, B3, C2, D1, E2, F1]

iii) Clinical Devices, Instrumentation and Statistics

- ***Synopsis***

It was the prospective publication of a paper based on a final year undergraduate degree project [G25] that initially generated an interest in research and, in the absence of any available research projects on myopia, I undertook a PhD in experimental psychology at City University, London (title: 'The role of colour in the utilisation of visual information'). The PhD incorporated training in experimental methodology, design and analysis which was applied to work at Aston University on various aspects of visual ergonomics and clinical instrumentation [G10-G18]. The PhD also involved assimilation of information theory which engendered a longstanding interest in statistical design and analysis [G22-G24].

Publications

G10. Pointer JS, Gilmartin B & Larke JR. The evolution of the broken ring visual acuity test figure. *J Am Optom Assoc.* 1980; 51:741-745. [A3, B3, C3, D2, E2, F3]

G11. Pointer JS, Gilmartin B & Larke JR. A device to assess visual performance with optical aids. *Am J Optom Physiol Opt* 1981; 58:408-413. [A3, B3, C2, D2, E2, F3]

G12. Flanagan JG, Wild JM, Barnes DA, Gilmartin B, Good PA & Crews J. The qualitative comparative analysis of the visual field using computer assisted, semi-automated and manual instrumentation: I Scoring system. *Doc Ophthalmol.*1984; 58:319-324. [A3, B2, C2, D2, E3, F3]

G13. Wild JM, Flanagan JG, Barnes DA, Gilmartin B, Good PA & Crews J. The qualitative comparative analysis of the visual field using computer assisted, semi-automated and manual instrumentation: II Statistical analysis. *Doc Ophthalmol.*1984; 58:325-340. [A3, B2, C2, D2, E3, F3]

G14. Flanagan JG, Wild JM, Barnes DA, Gilmartin B, Good PA & Crews J. The qualitative comparative analysis of the visual field using computer assisted, semi-automated and manual instrumentation: III Clinical analysis. *Doc Ophthalmol.*1984; 58:341-350. [A3, B2, C2, D2, E3, F3]

G15. Gilmartin B & Hogan RE. The magnitude of longitudinal chromatic aberration of the human eye between 458 and 633nm.*Vision Res.*1985; 25:1747-1753. [A1, B2, C1, D1, E1, F1]

G16. Linfield PB, Gilmartin B & Flanagan JG. Analysis of the effect of sun phantom on the conspicuity of directional green arrow traffic signals. In: *Vision in Vehicles* (Gale A, editor), Elsevier: North Holland, Amsterdam, 1986; pp 87-97. [A2, B2, C2, D1, E2, F2]

G17. Wood JM, Wild JM, Bullimore MA & Gilmartin B. Factors affecting the normal perimetric profile derived by automated static threshold LED perimetry. I. Pupil size. *Ophthal Physiol Opt.* 1988; 8:26-31. [A3, B2, C2, D2, E2, F3]

G18. Wood JM, Bullimore MA, Wild JM & Gilmartin B. Factors affecting the normal perimetric profile derived by automated static threshold LED perimetry. II. Accommodative microfluctuations. *Ophthal Physiol Opt.* 1988; 8:32-36. [A3, B2, C2, D2, E2, F3]

G19. Morgan AJ, Harper J, Hosking SL & Gilmartin B. The effect of corneal thickness and corneal curvature on pneumatonometer measurements. *Current Eye Res.* 2002; 25:107-112. [A2, B3, C2, D2, E2, F2] ***WoS* Citations = 31**

C20. Santodomingo-Rubido J, Wolffsohn JS & Gilmartin B. Comparison between graticule and image capture assessment of lower tear film meniscus height. *Cont Lens Ant Eye* 2006; 29:169-173. [A2, B3, C2, D2, E2, F1]

G21. Wolffsohn JS, Hunt OA, Naroo SA, Gilmartin B, Shah S, et al. Objective accommodative amplitude and dynamics with the 1CU 'accommodative' intraocular lens. *Invest Ophthalmol Vis Sci.* 2006; 47:1230-1235. [A3, B3, C2, D2, E2, F3]

G22. Armstrong RA, Eperjesi F & Gilmartin B. The application of analysis of variance (ANOVA) to different experimental designs in optometry. *Ophthal Physiol Opt.* 2002; 22:248-256. [A2, B2, C2, D2, E3, F3]

G23. Armstrong RA, Eperjesi F & Gilmartin B. The use of correlation and regression in optometry. *Clin Exp Optom.* 2005; 88:81-88. [A2, B2, C2, D2, E3, F3]

G24. Armstrong RA, Davies LN, Dunne MCM & Gilmartin B. Statistical guidelines for clinical studies in human vision. *Ophthal Physiol Opt.* 2011; 31:123-136. [A2, B2, C2, D2, E3,

iv) Ophthalmic and Systemic Drugs

- ***Synopsis***

From 1974 onwards, undergraduate teaching responsibilities at Aston University in ophthalmic drugs led to a series of papers on ocular adverse reactions to systemic and ophthalmic medication [G27, G29, G31, G32] with particular attention to myopia [G30].

Publications

G25. Austen DP, Gilmartin B & Turner P. The effect of chlordiazepoxide on visual fields, extraocular muscle balance, colour matching ability and hand-eye co-ordination in Man. *Brit J Physiol Opt.* 1971; 26:161-165. [A2, B2, C2, D2, E3, F3]

G26. Hogan RE & Gilmartin B. The relationship between tonic vergence and oculomotor stress induced by ethanol. *Ophthal Physiol Opt.* 1985; 5:43-51. [A2, B2, C2, D2, E1, F1

G27. Gilmartin B. The Marton Lecture: Ocular manifestations of systemic medication. *Ophthal Physiol Opt.* 1987; 7:449-459. [D1]

G28. Gilmartin B, Amer AC & Ingleby S. Reversal of tropicamide mydriasis with single instillations of pilocarpine can induce substantial pseudo-myopia in young adults. *Ophthal Physiol Opt.* 1995; 15:475-479. [A1, B2, C1, D1, E1, F3]

G29. Edgar DF & Gilmartin B. Ocular adverse effects of systemic medication. *Ophthal Physiol Opt*. (Supplement: *Clinical Optometry Update*) 1997; 17:S2-S8. [D1]

G30. Santodomingo-Rubido J, Gilmartin B & Wolffsohn JS. Drug-induced bilateral transient myopia with the sulphonamide sulfasalazine *Ophthal Physiol Opt.* 2003; 23:567-570. [A1, B3, C2, D1, E1, F1]

G31. Cox AR & Gilmartin B. Drug-induced ophthalmic adverse reactions. *Adverse Drug Reaction Bulletin* 2006; 241:919-922. [D1]

G32. Gilmartin B. The optometric management of ocular adverse reactions to systemic medication In: *Optometry: Science, Techniques and Clinical Management* (Rosenfield M & Logan NS, editors), 2nd Edition, Butterworth Heinemann: Oxford, 2009; pp.111-126. [D1]

- ***Examples of recent citations***

G6: Williams KM, Hysi PG, Nag A et al. Age of myopia onset in a British population-based twin cohort. Ophthal Physiol Opt. 2013; 33:339-345.

G7: Spitschan M, Jain S, Brainard DH, et al. Opponent melanopsin and S-cone signals in the human pupillary light response. Proc Nat Acad Sci USA 2014; 111:15568-15572.

G8 & G9: Kimura E, Abe S, Goryo K. Attenuation of the pupillary response to luminance and color changes during interocular suppression. J Vision 2014; 14:14.

G9: Lobato-Rincon LL, del Carmen Cabanillas-Campos M, Bonnin-Arias C et al. Pupillary behavior in relation to wavelength and age. Front Hum Neurosci. 2014; 8:221.

POSTSCRIPT

In addition to those publications cited in the submission as being *In Press* or *Under Review* pending publications are:

P1. Nagra M, Gilmartin B, Logan NS & Anderson SJ. The effect of retinal stretch in anisomyopia on ganglion cell density and receptive field size: a case study. Proc. R Soc Lond B *[A2, B2, C2, D2, E1, F1]*

P2. Nagra M, Gilmartin B, Dunne MCM & Logan NS. Concordance of retinal contour profiles derived using 3D MRI and peripheral refraction in adult human eyes. Invest Ophthalmol Vis Sci. [A2, B2, C2, D2, E1, F1]

P3. Buckhurst H, Gilmartin B, Cubbidge RP & Logan NS. In vivo measurement of regional variation in anterior scleral resistance using ballistic tonometry. Exp Eye Res. [A2, B2, C2, D2, E1, F3]

Caveat: The submission has addressed the aetiology of myopia with reference to aspects of structure, function and epidemiology and hopes that it contributes to further understanding of the bases for myopia therapy. Cessation of long-term therapy that commenced in the adolescent developing eye may, however, have pathological consequences should it provoke reversion to a predetermined myopic state as structural change is then likely to be induced in a fully developed adult eye.