Professor Robin Michael Winter BSc (Hons), MB BS, FRCP, FMedSci

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Introduction

Robin Winter, who died at the early age of 53 years from cancer of the oesophagus, combined exceptional clinical skills in facial and pattern recognition with an unusual facility for mathematics and computation. In the early 1980s he rapidly established himself as a world leader in the embryonic field of clinical dysmorphology: the recognition of rare syndromes based on characteristic combinations of facial appearance, associated malformations and neurodevelopmental profile. In his very busy practice as a clinical geneticist he described and elaborated many syndromes and provided an expert clinical opinion that was widely sought by the genetics community. He ensured the dissemination of his expertise by co-hosting regular informal meetings to discuss difficult clinical cases and by founding a new journal, *Clinical Dysmorphology*, of which he was co-editor. Arguably his most important single contribution was to develop a computer database, the London Dysmorphology Database, as an expert aid to diagnosis: this is used by clinical geneticists and paediatricians worldwide and has been adopted as a model for several other clinical diagnostic databases.

Winter always placed his clinical insights in a scientific context. His mathematical facility enabled him to develop, and promulgate, rigorous Bayesian approaches to the calculation of genetic risks. He was at the forefront of the application of molecular genetic techniques to carrier testing and prenatal diagnosis of X-linked disorders, and collaborated in the identification of precise molecular genetic bases for several classical dysmorphic syndromes, notably those involving craniosynostosis. Very early on he realised that mouse mutants might provide direct genetic equivalents for some of these human syndromes and was triumphantly vindicated by subsequent molecular

findings. Overall, his work contributed significantly to the fundamental insight that orthologues of genes involved in patterning of model organisms also play key roles in human development, in both health and disease.

Career background and early influences

Winter was born into a medical family in the Wirral, near Liverpool, England (his father was a consultant radiologist and his brother is a consultant haematologist), and went to school at Malvern College. After passing his A levels he was still too young to start his medical training; during his gap year he looked after laboratory rats, an experience that initiated his interest in development and malformation, and the use of rodents to study these processes. He went to University College London (UCL) to read medicine, won prizes for medicine and neurology, and decided to undertake an intercalated BSc in Genetics at the Galton Institute. Here he was influenced by, amongst others, Hans Grüneberg, a pioneer of mouse developmental embryology, Cedric ("CAB") Smith, who developed mathematical methods to analyse genetic linkage, and Gerald Corney, whose interests included twinning and malformation. These experiences cemented his determination to become a clinical geneticist, which at this time (mid-1970s) was still an ill-defined specialty, practised by only a handful of consultants in the UK, and without a clear career pathway.

Far from being deterred, Winter took advantage of this flexibility to create his own opportunities. When gaining experience in paediatrics as a Senior House Officer at Harperbury Hospital, Radlett, Hertfordshire, he met Michael Baraitser, a visiting neurologist. He persuaded Baraitser to tutor him for the Membership of the Royal College of Physicians (MRCP) exam, the first episode in what was to prove a life-long collaboration. After passing the MRCP, Winter secured an 18-month fellowship

(1977-78) at the new Department of Human Genetics established by Walter Nance at the Medical College of Virginia, Richmond, USA. Here he was able to immerse himself in all aspects of human genetics, published his first paper, and attended the genetics course at Bar Harbor organised by Victor McKusick. By the time he returned to the UK, his plan to develop a database of genetic syndromes was already forming.

Winter's return to the UK was perfectly timed, enabling him to take up one of the first three Senior Registrar posts to be created for Clinical Genetics (Dian Donnai and Ian Young were the two other trainees). Back at the Harperbury Hospital he renewed contact with Baraitser, spawning a remarkable 25-year collaboration to develop and update the London Dysmorphology Database (LDDB) that terminated only with Winter's death. Winter's publications whilst still a Senior Registrar immediately marked him out as an exceptional talent, those in 1980 ranging from Bayesian risk calculation with Fortran computer programming (2,4,8) to pure clinical dysmorphology (3,7).

In April 1981 Winter became a Consultant Clinical Geneticist at the Kennedy-Galton Centre (Northwick Park Hospital) at the remarkably early age of 30 years. From the outset he was funded part-time by the UK Medical Research Council as a scientist at the Clinical Research Centre and in 1988 established the Dysmorphology Research Group. This enabled him to pursue his diverse interests in genetic linkage, computer databases, the molecular genetics of dysmorphic syndromes and syndrome identification. He maximised his clinical exposure by travelling down to the Hospital for Sick Children, Great Ormond Street every Thursday for a joint clinic and ward round with Baraitser.

Pedigree analysis, risk calculation and X-linked disorders

Winter's computational abilities and Galton Laboratory training led him to take a rigorous mathematical approach to genetic risk estimation using Bayesian methods. For example, early work on calculation of the ratio of male to female mutation rates (4,12,22) led to an abiding interest in the complexities posed by X-linkage. This background placed Winter, in collaboration with Marcus Pembrey and Kay Davies, in an excellent position to analyse some of the earliest applications of linked restriction fragment length polymorphism (RFLP) markers to carrier and prenatal risk estimation. In 1984, with Edward Tuddenham, they identified an RFLP for probe DX13 that enabled the first carrier tests for haemophilia A (33) and subsequently described the prenatal diagnosis of this disorder (37,44). It was soon realised that use of markers flanking the disease locus was desirable to avoid errors due to recombination and Winter explained the appropriate methods to analyse this (38). Later, Winter combined his scientific knowledge, clinical acumen and counselling skills to help families segregating Pelizaeus-Merzbacher disease, an X-linked disorder caused by mutations or duplications of the *PLP1* gene. In one instance, attention to the significance of a variant band seen on single strand conformation polymorphism (SSCP) analysis, then a novel technique, prevented a termination of pregnancy and thereby saved a healthy male fetus (120). Complex counselling issues were also raised in the pregnancy of a woman simultaneously mosaic for a *PLP1* duplication and an unrelated Xq deletion (264).

A further influential contribution was to the genetics of fragile X syndrome where, noting that the pedigree data were not compatible with classical X-linked inheritance, Pembrey, Winter and Davies suggested the presence of a "premutation" which only converted to a full mutation when the X chromosome carrying the premutation was

inherited and transmitted by a female (40). The premutation idea was both influential and controversial, leading Winter and colleagues to expand on it in several further papers (46,53,55,58,66). Although the ingenious proposal that recombination (which would be possible only in the female) was required to convert the premutation to a full mutation (40,55) turned out to be incorrect, the underlying triplet repeat mechanism was guessed by no-one until its discovery several years later (Kremer et al. 1991).

Development of computerised databases

Joining forces with Baraitser, Winter combined his computing and dysmorphology expertise to develop a computerised database of dysmorphic syndromes. The first publication reporting this work, dating from 1984, concluded that "The system is easy to update and two clinicians spending a couple of hours a week can easily achieve this" (30). Such was the success of the LDDB, and the growth of clinical dysmorphology as a specialty, that within a few years this statement was far from the truth. The constant updating of the database was only achieved through close liaison with Baraitser and ceaseless toil outside normal working hours.

Winter's computing knowledge and organisational skills enabled him to drive new developments of the database. Initially the disks were privately distributed to colleagues, but from 1990 new versions of the LDDB were released by Oxford University Press, an early venture in electronic publishing (D1). Correctly anticipating that compact disks would provide a powerful technology for increased memory storage, pictures on CD-ROM were added in 1993 (D8). The LDDB has been hugely successful, being used by clinicians all over the world and being updated frequently for new editions. More than any other factor it helped to put clinical dysmorphology

on a sound academic footing and has assisted greatly both in the identification of new syndromes (for example, 48,89,71) and in the better delineation of existing ones (for example 64,87,101). The London Neurology Database (also a collaboration between Baraitser and Winter; 86,D2) was written according to a similar structure: several further organ-specific databases have been developed by others as clones of the original concept.

Winter's fascination with computational approaches to dysmorphology persisted throughout his career and his contribution was probably unique, because few others could embrace expertise in such diverse fields. His interest in mouse models of malformation (see next section) led him to develop a computerised mouse malformation mutant supplement (74,D3) and later, a web-based resource (172). More recent interests included the incorporation of information on murine developmental expression patterns (with Jonathan Bard; 245,286) and the use of 3D analysis of facial morphology to explore the possibility of automation for the diagnosis of dysmorphic syndromes (with Peter Hammond; 281) and as a research tool to provide a methodology to compare individual patients with the average for a specific syndrome.

The molecular basis of dysmorphic syndromes

In the late 1980s, whilst still at the Kennedy Galton Centre, Winter was one of the first people to start thinking about how one might identify the molecular basis of dysmorphic syndromes: an immense challenge at that time. He had the great foresight to obtain funding to collect samples from large cohorts of patients long before the techniques were available for analysis. In 1988 he produced two brilliant insights into Greig cephalopolysyndactyly (GCPS) syndrome that provided a model for the

approach subsequently taken to many other dysmorphic syndromes. First, a systematic search for similarities between known mouse malformations and human dysmorphic syndromes (75) led him to propose the extra-toes (*Xt*) mouse as a genetic model for GCPS (76). Second, noting that two balanced chromosomal translocations involving 7p13 were associated with GCPS-like phenotypes, he demonstrated (with Louise Brueton, then his MD student, and Robert Williamson) significant genetic linkage in seven families segregating the disorder to this same region of chromosome 7 (77). This work led others to discover that mutations in GLI3 cause GCPS in humans (Vortkamp et al. 1991) and the *Xt* phenotype in mice (Hui and Joyner 1993), triumphantly vindicating his earlier conclusions.

During this period Winter also became interested in the molecular basis of craniosynostosis. Along similar lines to his previous thinking on GCPS, he hypothesised that terminal deletions of 7p that were associated with craniosynostosis showed features similar to Saethre-Chotzen syndrome (SCS). Analysis of SCS families by Brueton with DNA markers on 7p indeed showed significant linkage (117). Around this time Winter moved to the Institute of Child Health, London and developed a highly successful collaboration with Sue Malcolm and Willie Reardon on the genetics of craniosynostosis. The identification of genetic linkage of Crouzon syndrome to 10q26 (Preston et al. 1995) heralded a rush of disease gene identifications in the fibroblast growth factor receptors (FGFRs) using a positional candidate approaches. Mutations of *FGFR2* in Crouzon syndrome (152), *FGFR1* in Pfeiffer syndrome (with Maximilian Muenke; 150,153) and of *FGFR2* in Apert and Pfeiffer syndromes (with Andrew Wilkie; 157,158) occurred in rapid succession, producing several of Winter's most highly cited papers. Detailed follow-up work on these FGFR mutations yielded a wealth of publications (164,179,183,194,226,273).

The molecular basis of SCS also seemed within reach, with the identification of several apparently balanced chromosome translocations (128,151,160) seemingly providing a resource for positional cloning. As it turned out, none of these translocations precisely disrupted the responsible gene, *TWIST1* (193), and the first mutations were reported by two other groups (Howard et al. 1997, El Ghouzzi et al. 1997). Although this was certainly disappointing to Winter, he was not inclined to dwell on such matters and in any case could console himself that the critical clue to this successful identification came from precisely the mouse-human homology mapping approaches that he had so strongly advocated.

By the late 1990s, as Winter had anticipated in several reviews (167,171,185), the identification of disease genes for human malformation was transformed from a Cinderella pursuit to a mainstream activity. Winter collaborated with Peter Scambler at the Institute of Child Health in the identification of several further new disease genes. 1998 saw the identification of mutations of *SHOX1* in Leri-Weill dyschondrosteosis (204,235,258); in 2003-5, mutations in *FRAS1, GRIP1* and *FREM2* were shown to cause Fraser syndrome (270, Takamiya et al. 2004, Jadeja et al. 2005). These latter discoveries were another triumph for Winter, who had correctly proposed 15 years earlier that all three of the corresponding mouse mutants blebbed (*bl*), eye-blebs (*eb*) and myencephalic blebs (*my*) could be models of Fraser syndrome (75,105). Fortunately he lived to see his predictions vindicated. Amongst many other significant contributions that he made to the genetic mapping and/or disease gene identification of dysmorphic syndromes, his inputs into MASA syndrome (92,146), synpolydactyly (192,211) and oral-facial-digital syndrome type 1 (191,240) were particularly noteworthy.

Cleft lip and palate, subtelomeric disorders

Winter had relentless curiosity and wanted to get to the bottom of all the conditions that he encountered. To complement his interest in monogenic disorders, he made considerable efforts to unravel the complex genetic basis of cleft lip and palate (CL/P) and made important clinical contributions to early work on finding patients with subtelomeric abnormalities.

From 1991 until his death, Winter (in collaboration with Malcolm) successfully applied for five project grants to work on CL/P. This represented one of the most significant efforts worldwide, sustaining the field during the 1990s. Although progress was modest compared to the dramatic advances in elucidating the causes of monogenic disorders, Winter and Malcolm managed a good publication output despite frequently negative findings (115,130), focusing attention on possible associations of CL/P with *TGFA* (116,149) and later with *MTHFR* (256). Most importantly, Winter's group undertook the first genome-wide linkage analysis of affected sib pairs with CL/P, yielding a number of suspected linkages meriting further scrutiny (230). A report that popliteal pterygium was allelic with the Van der Woude syndrome locus on 1q32 (224) was vindicated when mutations in *IRF6* were later identified (Kondo et al. 2002).

Also in the early 1990s, Winter became interested in the attempts led by Jonathan Flint to identify abnormal dosage of subtelomeric regions as a possible cause of learning difficulties. Confirming the validity of the approach, three such patients were identified in the initial screen, two of whom were from Winter's clinic (156). Winter collaborated enthusiastically in follow-up studies by the Oxford group (223) and later hosted Bert de Vries at the Institute of Child Health who described several further patients in case reports (234,237,242) and developed a clinical check-list to prioritise

patients for screening (236). Not surprisingly Winter also ensured that his patients had early access to new comparative genomic hybridisation microarray techniques (279).

Clinical case reports

In addition to these specific themes, Winter published a very large number of clinical case reports. Underlying this was a quiet determination that all his (and other people's) patients deserved the best possible opinion on their diagnosis and its clinical and genetic implications, and that the best way to achieve this was to maximise communication about rare clinical entities. In the first half of his career Winter published many of these reports in *Journal of Medical Genetics*, but as time went on it became more difficult to do so. He recognised the need for a specialist dysmorphology journal and in 1992 founded, with Baraitser and Donnai, the journal *Clinical Dysmorphology*. This soon established itself as the key specialist journal in the field and he continued as co-editor until his death. As an important adjunct, regular (3 or 4 per year) UK Dysmorphology Club meetings were held at the Institute of Child Health: these enabled informal review and matching of interesting cases (for example, 190).

Collectively Winter's case reports, allied to the regular updating of the LDDB, advanced the classification of many different disorders. Although he had no personal interest in such matters, two syndromes that he described now bear his name in their eponymous titles. Appropriately, one of these is the Baraitser-Winter syndrome (OMIM 243310) (72;276); the other is MacDermot-Winter syndrome (OMIM 247990) (85). Others will doubtless follow.

Later career and personal background

Winter had a long-standing connection (holding Honorary Consultant status) with the Institute of Child Health and Hospital for Sick Children, Great Ormond Street, where Baraitser worked. Eventually he moved there in 1992, first as Reader and, from 1994, as Professor of Dysmorphology and Clinical Genetics. With its very busy clinical practice this was the ideal location for him, as this was the driving force behind all his work: as a result of his expertise, many patients and families were given a secure diagnosis for the first time. Despite mounting managerial and external responsibilities, Winter resisted the pressures to reduce his clinical practice. Indeed he probably became even more busy because, in a field where diagnosis requires arcane knowledge and subjective judgement, Winter's opinion reigned supreme. He received many tertiary referrals from other clinical geneticists and the era of electronic communication made him easily accessible by email as well. Such was his dominance that, when discussing a difficult diagnostic case, the question "has the patient seen Robin?" would frequently come up. If the answer was yes, and *he* had failed to make a diagnosis, this carried the implication that the diagnostic process had reached the end of the road.

Despite his very busy schedule Winter shouldered a heavy and uncomplaining burden of administrative matters, for example as Council member for the Royal College of Physicians and the Clinical Genetics Society, of which he was latterly the President (2000-2002). In addition to co-editing *Clinical Dysmorphology* he served on the editorial boards of *Journal of Medical Genetics*, *Archives of Disease in Childhood* and *European Journal of Human Genetics* (as clinical genetics section editor). He had stints on the scientific advisory boards of the Medical Research Council, the Birth Defects Foundation and Action Research, amongst others.

Winter was elected Fellow of the Academy of Medical Sciences in 2000 and was honoured with several national and international awards, which he accepted with gracious but self-deprecating humour. Amongst these were the Royal Society of Medicine Medical Book Awards (1995) and BMA Medical Book Awards (1998) for his electronic databases; the Maria Vilma and Bianca Querci Foundation Prize for Paediatric Research (1997-2000) and the Baschirotto Prize of the European Society of Human Genetics (2001). He was invited to give many keynote talks including those at the 1st Annual Meeting of the American College of Medical Genetics (1994), the Distinguished Speakers' Symposium of the American Society of Human Genetics (1994), and, for an International Symposium on craniofacial malformations, at the US National Institutes of Health (1998).

Winter's time outside work was very orientated towards his family and his happy domestic life undoubtedly contributed towards his professional success. He met Joan, his future wife, in Liverpool whilst they were undertaking summer jobs there, discovering that they were also both undergraduates at UCL. They married in 1973, whilst Winter was still a medical student. Joan graduated in German and qualified as a teacher. They had two children, Amy and Henry. Winter always took leave during the school holidays and was proud of his children's achievements.

In character he was modest and quietly spoken, having no interest in the trappings of academic promotion. Superficially shy, he had a wry sense of humour that shone through both in personal conversation and in his invited lectures. His health suffered a setback in 1998 when he had a mild myocardial infarction; he coped with this with fortitude and, although reducing his commitments a little, still managed a formidable work rate until his final illness.

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