IN MEMORIAM

Eric Engel

Geneva, 12 October 1925 - Geneva, 9 September 2011

It is with a sense of great privilege and a feeling of sadness that I commemorate Eric Engel, M.D., a pioneering geneticist, a former professor at Geneva and Vanderbilt Universities, and an Emeritus Professor of Geneva University, who died on September 9, 2011 at the age of 85 in his native Geneva.

There are many reasons for feeling privileged. Eric Engel was a man of extraordinary stature, a giant on whose shoulders also small researchers could see far away. He was a world renowned scientist whose name is sculptured in the history of Human and Medical Genetics and who transcended the borders of the contiguous disciplines fostering the entire field of Medical Sciences.

Most of all, Eric will be remembered by cytogeneticists from all over Europe, as he was particularly close to the E.C.A., to its past and present board members and presidents. He attended all E.C.A. conferences as long as he could, actively participating in the scientific work and brightening up the social events with his charming, cheerful presence. When Professor Eric Engel was appointed an honorary member of the E.C.A. in 2002, it was my honour to write a short profile of him for the E.C.A. NL (No 10, July 2002). I am particularly proud that Eric sent me a hand-written letter appreciating my text and showing what a thoughtful and sympathetic person he was. At the Fourth European Cytogenetics Conference (6-9 September, 2003, Bologna, Italy) Eric gave the Opening Lecture entitled: "Some lessons from UPD in the framework of contemporary cytogenetics and molecular biology". He captured the audience with his fascinating synopsis of the merging fields of cytogenetics and molecular biology, anticipating the notion of the molecular karyotype.

My feelings of sorrow are associated with the loss of a great person who was committed to his institutional tasks and to his patients, a scientist who influenced my historical and perspective vision of the field of human genetics and gifted me with friendly competent and inspiring conversations on art and humanities. Our thick correspondence continued till the 5th of August 2011, date of the last letter I received from him, which revealed a trembling calligraphy but a lucid analysis of the inexorable evolution of his disease.

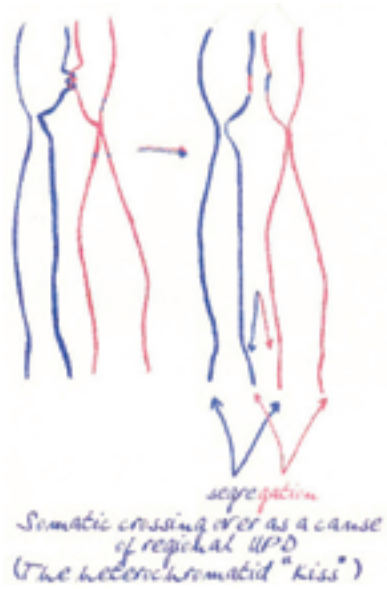

Fig. 1 A sketch of E. Engel to outline the "heterochromatid kiss" underlying segmental UPD

Eric Engel was born in Geneva on 12 October 1925. He was educated at the Medical School of Geneva where he earned his medical degree in 1951 and received residence training in endocrinology at the Geneva University Hospital (1951-1960). In 1960, following a visit to the laboratory of Dr. J. Lejeune in Paris, he accepted positions as an instructor in Medicine at the Harvard Medical School and as a clinical and research Fellow at the Massachusetts General Hospital, where he distinguished himself in the field of cytogenetics. In the period 1960-63 he set up a laboratory for the study of chromosomes, shifting the approach from fibroblasts to short term blood cultures. His main interest focussed on sex chromosome anomalies of endocrine patients, who provided him with a unique opportunity of studying the first described cases of Klinefelter and Turner syndromes.

In 1963 one of the world's leading endocrinologists, G.W. Liddle recruited him to the Vanderbilt University School of Medicine to help establish a medical genetics unit and direct the cytogenetics lab. Dr. Engel was named professor of Medicine, associate

professor of Pediatrics and director of the Division of Genetics. During the long and very active period at Vanderbilt (1963-1978) he promoted the development of genetics, addressed the study of chromosomal changes in both constitutional pathology (birth defects and congenital disorders) and hematological malignancies (chronic myeloid leukemia, promyelocytic leukemia), and contributed to the mapping of human genes by the novel tool of somatic cell hybrids. By the early 1970s he had developed a reputation as one of the few leading cytogeneticists in the country.

Despite being a recognized leader of basic science research projects he always maintained his initial preference for clinical experience, nurtured by the constant practice of genetic counselling. As Director of the Genetics Center he worked on the problems of infertility and recurrent abortions in the first trimester. It was the high rate of chromosomal aberrations in early pregnancy losses that stimulated his first reflections on the potential for complementation of gametes that are nullisomic and trisomic for the same chromosome. This seminal breakthrough, which can be traced back to his last years at Vanderbilt University, was the first conceptual framework for thinking about Uniparental Disomy, the presence in a diploid genome of a chromosome pair derived from one parent. The concept was subsequently extended to include two alternative mechanisms, trisomy and monosomy rescue through chromosome loss or duplication following maternal non disjunction events, which accounted for UPD in the two forms of heterodisomy and isodisomy.

In 1979 Eric Engel moved back to Geneva to direct the University Institute of Medical Genetics. He further elaborated on the concept of uniparental disomy with its attendant risk of recessive disorders, a risk later compounded by the occurrence of imprinting disorders. Following a long inspired night in June 1979, he presented the concept of UPD in a paper submitted to the American Journal of Medical Genetics which was published in 1980[1]. At that time its implications were speculative, as adequate molecular evidence was not yet available. As commented by Eric Engel in one of his last papers[2] "Once masterly edited by John Opitz, and accepted after a long wait for publication, the paper slept on a shelf for several years, for want of the molecular developments which would make it possible to tell the parental origin of the chromosomes from their DNA polymorphisms." Credit must be given to John Opitz, the Editor of the American Journal of Medical Genetics, for publishing a pioneering concept that awaited some 7 to 8 years for clinical and molecular confirmation[3]. The case with Cystic Fibrosis and maternal UPD7 reported by the group of A.L. Beaudet was just the first of a long series of some 40 examples of such transmission of a recessive trait that were reviewed by Eric Engel in 1996[2]; there are many more of such "mendelian recessive outlaws" reported in the current literature. Furthermore, several imprinted chromosome domains and loci have been, for a large part, identified through different UPDs as "at the biological level the loss or duplication of monoparentally expressed allele sequences constitutes imprinting rights infringements" [2]. Segmental UPD, resulting from balanced somatic crossing over (Fig.1) appeared to be a hallmark in a proportion of patients with imprinting growth disorders. It was subsequently also demonstrated as a part of the clonal evolution of human malignancies.

Eric Engel spent the last decade of his academic and professional career in Geneva where he set up a DNA analysis laboratory in 1984 to support the interdisciplinary clinical-cytogenetic direction of the Medical Genetics Institute. He concentrated his activities on uniparental disomy and genomic imprinting, keeping up with all the new published evidence and critically reviewing the enormous body of data contributed from all over the world. He retired in 1991 and was succeeded by S.E. Antonarakis. He continued to be involved in science, and to be a prolific writer. His activity was reflected in numerous reviews and lectures and the world renowned book written together with Stylanos Antonarakis on "Genomic Imprinting and Uniparental Disomy in Medicine" [4].

The name of Eric Engel is indissolubly linked to the seminal concept of UPD. The serendipitous inspiration of this concept was a result of cross-fertilization of clinical experience with basic research interests in the field of constitutional chromosomal aberrations. The impact of this mechanism, at the root of human pathology, on prenatal and postnatal diagnostics has been incredible. This mechanism is essential for the understanding of genomic imprinting and the mechanisms associated with tumorigenesis and tumor progression.

Eric was not only a talented scientist, he was also a person of exceptional culture, a "connaisseur" of arts and a cordial and friendly interlocutor.

Thank you Eric for the gifts you have given us in Human and Medical Genetics and beyond!

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1 Engel E: A new genetic concept: uniparental disomy and its potential effect, isodisomy. Am J Med Genet 1980; 6: 137–143.

2 Engel E: A fascination with chromosome rescue in uniparental disomy: Mendelian recessive outlaws and imprinting copyrights infringements. Eur J Hum Genet 2006, 14, 1158–1169.

3 Spence JE, Perciaccante RG, Greig GM *et al*: Uniparental disomy as a mechanism for human genetic disease. Am J Hum Genet 1988; 42: 217–225.

4 Engel E, Antonarakis SE: Genomic Imprinting and Uniparental Disomy in Medicine (Clinical and Molecular Aspects). Wiley-Liss Inc., New York, 2002, pp 1–285.