Genomic Imprinting and Uniparental Disomy in Medicine
Genomic Imprinting and Uniparental Disomy in Medicine
Clinical and Molecular Aspects

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In 1980, Eric Engel proposed a new concept in clinical genetics—uniparental disomy (*Am J Med Genet* 6:137). From the known information regarding chromosomal abnormalities and spontaneous abortions, he emphasized that it was “statistically likely and foreseeable” that uniparental disomy (UPD) would occur from the union of a disomic gamete with a gamete nullisomic for the same chromosome. He correctly anticipated the potential for male-to-male transmission of an X-linked trait and the likelihood of homozygosity for recessive mutations by virtue of a common origin for part or all of two chromosomal homologs. His ability to anticipate the occurrence of UPD was remarkable. We now know that trisomy or monosomy rescue are also important mechanisms for the occurrence of UPD.

Also in 1980, there were two reports (*Clin Genet* 17:418 and 18:456) of the transmission of a translocation (22q;22q) from a mother to a normal daughter. In both cases, it was hypothesized that the normal daughter had either resulted from a trisomic zygote with rescue or from gametic complementation through fertilization of a disomic oocyte by a nullisomic sperm. Clearly these reports represented UPD in the context of an abnormal karyotype. In 1984, there was a report (*Am J Hum Genet* 36:123) of four cases of mosaic Down syndrome; it was concluded that in at least two and possibly three of these individuals, the diploid cell lines represented UPD for chromosome 21. These could be described as a mosaic trisomy rescue. UPD with a normal chromosome analysis was given little attention until we had the remarkable opportunity to see a patient with cystic fibrosis and maternal UPD for chromosome 7 (*Am J Hum Genet* 42:217, 1988).

By now it is clear that our report of the first documented case of uniparental disomy with a normal karyotype in 1988, while searching for something entirely different, has proven to be a career-altering event for me. The story begins at a North
American Cystic Fibrosis Conference in what must have been Fall of 1986. The CF gene had been mapped to chromosome 7, and a small group of human geneticists were providing didactic sessions on the new potential to use linkage analysis and linkage disequilibrium data for prenatal diagnosis and risk assessment. I asked the large gathering of clinicians and caregivers for help in identifying any patients with cystic fibrosis and other clinical abnormalities. The plan was to find a patient with a small deletion that would allow our research group to be the first to identify the CF gene. This was not to be, but Dr. Ronald Perciaccante told me of a patient of his who had been reported in 1980, the year of Eric Engel’s proposal for UPD, to have short stature and growth hormone deficiency (Am J Dis Child 134:317). I was swift to visit Dr. Perciaccante in upstate New York near the Canadian border where he hosted me in his home. At his office, he introduced me to a young woman with CF and her father; unfortunately her mother was deceased.

I enthusiastically collected blood and rushed to Houston where Ed Spence, a clinical fellow in the lab, performed Southern blotting and found that the patient was homozygous or hemizygous for more than one RFLP while her father was apparently homozygous for the corresponding alternate allele. Given a normal karyotype performed in David Ledbetter’s laboratory, two explanations seemed most plausible. Either the patient had a de novo or inherited deletion that might help lead us to the CF gene, or her father was not her biological parent. Dr. Perciaccante avowed that nonpaternity was implausible, and DNA markers, other than those on chromosomes 7, proved him correct. The deletion hypothesis was suspect from the beginning because the dosage, as crudely assessed on Southern blots, did not appear consistent with haploidy for the markers. It is difficult to recall the exact circumstances when the correct answer fell into place, but a collaboration with Hunt Willard for analysis of centromeric alphoid repeat polymorphisms was a turning point. The data strongly suggested that the patient had inherited two identical copies of the centromeric region of chromosome 7 from her maternal grandmother.

We encountered many skeptics, but three aspects of the literature at that time were remarkable. First, Eric Engel had wrestled with the possibility of UPD in humans as a theoretical topic some seven or more years earlier, and he had laid down the concepts and nosology for us. Second, there were published cases of presumptive UPD in the context of an abnormal karyotype as noted above. Third, there was extensive relevant and reassuring information becoming available in mouse genetics. The occurrence of UPD in the context of a normal karyotype gave an inkling of the various forms of unusual or nontraditional inheritance that would grow to include occult gonadal mosaicism for mutations, anticipation in triplet repeat disorders, and others.

Our report was surrounded and followed by a few low points including a rejection letter from Science, a commentary suggesting that UPD was unlikely to be anything more than an interesting rarity, and our failure to recognize the potential for UPD to cause Prader-Willi syndrome. Although David Ledbetter and I were regularly discussing UPD and the possible etiologies for the nondeletion cases of PWS, we left it to Rob Nicholls to put two and two together in 1989 (Nature 342:281).
There have been compensatory highs, and the opportunity to comment on this outstanding contribution by Eric Engel and Stylios Antonarakis is one of the most pleasant. As they so thoroughly document, UPD is now recognized as a clinically relevant occurrence that can affect the majority of human chromosomes, and maybe even all the chromosomes if one considers the possibility of UPD causing spontaneous abortions. The authors complement each other well, and they represent the lineage of human genetics in Geneva. *Genomic Imprinting and Uniparental Disomy in Medicine* will stand as a landmark contribution in biology and medicine. The book thoroughly documents the early years of the recognition of the importance of genomic imprinting and uniparental disomy in human biology and medicine. The book focuses on UPD but the ties to various other aspects of genomic imprinting are inevitable.

UPD has served as the clinical entry point into genomic imprinting in humans. Where is the field of human epigenetics today and where is it headed? Having just returned from two Gordon Conferences on human genetics and epigenetics, I am exhilarated by the prospect that we have barely scratched the surface of the importance of genomic imprinting in human variation and in evolution more generally. There are hints that autism might soon merit a chapter in future books reviewing imprinting, since maternal but not paternal duplications of chromosome 15q11-q13 cause the condition (*Am J Hum Genet* 60:928, 1997). Since genes affecting behavior seem to be imprinted in some cases, perhaps nontraditional inheritance has a major role to play in the etiology of psychiatric disease. There are suggestions that “genomic imprinting may have facilitated a rapid non-linear expansion of the brain, especially the cortex, during development over evolutionary time” (*Brain Res Dev Brain Res* 92:91, 1996). While UPD is just one part of the story of genomic imprinting and epigenetics in humans, the broader view suggests that there are many important discoveries yet to be made. The comprehensive and authoritative character of this volume lays down the gauntlet for future editions of this or similar texts. I expect that it will soon be inconceivable that one could undertake to cover all of genomic imprinting as it relates to medicine in a single book.

Arthur L. Beaudet

Baylor College of Medicine
In the field of human development, disomies occasionally arising from a single parent have their ugly side as well as some fascinating aspects. They challenge the traditional path of normal chromosome transmission through various mechanisms, among them: pathologically altering parental gene expression in an offspring, preventing the ill-effects of a trisomy or monosomy by “rescuing” them, and bringing about recessive traits or taking part in an oncogenic process. As such, these peculiar disomies have helped us to understand some new rules in the ever-evolving field of human inheritance. It is the purpose of this book to illustrate the various facets of this major but, until recently, unknown chromosomal aberration.

The emphasis of this book is on the clinical manifestations of known phenotypes related to uniparental disomy or genomic imprinting. It is likely, however, that not every clinical phenotype related to these two conditions is known, and that others will be added as our knowledge increases. The field is in full development and evolution, with a more complete understanding of molecular mechanisms and numerous other unanswered questions still to come. Moreover, molecular mechanisms presented herein may be modified as investigators continue to uncover more mysteries. It would give us pleasure if some readers become themselves contributors in the elucidation of the molecular pathophysiology of disorders related to uniparental disomy and genomic imprinting.

The authors are in different ways indebted to colleagues and friends whose inspiration, help, or participation played a decisive role in their work. It is E.E.’s utmost pleasure to acknowledge the people, who made it possible to establish and render credible the once far-fetched concept of UPD. John Opitz, some 20 years ago, called attention to it by publishing an article in the *Journal of Medical Genetics*, the
budding idea of which was then based on purely circumstantial evidence derived from the high frequency of gametal aneuploidy in humans. This article, entitled “A new genetic concept: uniparental disomy and its potential effect, isodisomy,” was planted into a risky and unbroken speculative ground. That seed only came to fruition when Arthur Beaudet and his colleagues gave it, in 1988, clinical life, by uncovering and describing the first clinical story of a disease due to uniparental disomy for the maternal chromosome 7. Tribute is also paid to the Wiley Editor of this book for advising its initiator (E.E.) to team with a molecular geneticist to carry out the task of writing it.

It was S.E.A. who, in the midst of so many major endeavors, enthusiastically took on this task and invigorated and endowed our work with his command of the molecular biology and the power of his brilliant intellect. Then, others joined the undertaking when the seas were rough and helped to bring it to shore. Celia Dawn Delozier and Robert Lyle are foremost among them, in contributing one chapter each and giving skilled advice.

One also thinks of other friends and colleagues who, without being directly involved, personally influenced the thinking of the authors or the progress of the field, a few of whom only can be named: Drs. Suzanne B. Cassidy, Patricia Jacobs, Rowena James, I. Karen Temple, Joan Knoll, Susan Malcolm, Wendy Robinson, Lisa Shaeffer, Karen Buiting, G. Gillessen-Kaesbach, Ellen Magenis, Susan L. Christian, Claudine Junien, David L. Ledbetter, Albert Schinzel, Robert Nicholls, Daniel Driscoll, Kurt Hirschhorn, Bernard Horsthemke, and closer to us, in Geneva, Siv Fokstuen and Armand Bottani. While many others could be named, those who most deserve E.E.’s final words are all the patients, wherever in the world, their parents and caretakers without whom medical history could not be written by their many humble and compassionate medical observers.

It was S.E.A.’s great pleasure to have the opportunity to work with E.E. on this project. When Eric asked me to share the responsibility for the development of this book, I saw it as an opportunity to learn from him and as an historical necessity. Professor Engel is my predecessor in the Chair of Medical Genetics of the University of Geneva Medical School (he himself took the torch from Professor David Klein). What a better way to establish a long-term link and friendship than by agonizing over the various chapters of a book together? Another attraction for participating in this effort was that it provided me with an opportunity to learn more about a fascinating truth that every toddler knows all too well: the father and the mother are not indeed the same, and that both are needed for a healthy development. As I consider myself an eternal student, the pleasure was substantial and continuous: every paper mentioned in the book was an eye opener and teaching tool. My thanks therefore naturally go to Eric Engel for his generous offer to share his exciting obsession, to all the clinical and basic investigators for all the new information they offer to their colleagues, readers, medical caretakers and patients, to all the members of the Division of Medical Genetics for their help, to Drs. C. DeLozier and R. Lyle for their insightful contributions to two chapters, and to all the patients and their families for their confidence in our ignorance and assistance in our curiosity. We also
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STYLIANOS E. ANTONARAKIS