Preface

Despite a recent report that some aneuploid strains of yeast are at a growth advantage under certain conditions, aneuploidy essentially remains a lethal condition. In humans it is the most common cause of death from the moment of conception onwards. This themed issue of the journal has articles that explore the causes of this exceptionally high incidence of aneuploidy in our species and the effects at different life stages. The issue is divided into three main sections: Aneuploidy at Different Life Stages, Genetic Regulation of Chromosome Segregation and Environment and Epigenetics.

In the Gametic subsection of Aneuploidy at Different Life Stages, two articles by Templado et al. and Perrin et al. explore the overall incidence of aneuploidy and of DNA fragmentation in men that are carriers of constitutional chromosomal anomalies. Fragouli et al. and Obradors et al. cover the findings in studies on oocytes, while Vialard et al. review the evidence for predisposition to aneuploidy in the female. Taking together the incidence of aneuploidy in sperm (4.5%) with the overall incidence in oocytes (20%), this suggests that around 25% of conceptions will be affected by meiotic aneuploidy. In women at least, this incidence is of course markedly affected by age. The final item in the Gametic subsection is a review of current literature relating to inherited aneuploidy due to germinal mosaicism by Delhanty; considered to be a rare event, recent evidence shows that it may be more common than previously perceived.

This figure of 25% at conception is, however, dwarfed by the incidence of aneuploidy in the in vitro-derived preimplantation embryo. In the Embryonic and Prenatal subsection, two articles cover aneuploidy at the cleavage stage (days 1–3), Mantzouratou and Delhanty, and at the

blastocyst stage (day 5–6), Fragouli et al. On average, by the time these embryos are 3 days old, 60% will have at least one aneuploid cell, but the great majority will be cases of mosaic aneuploidy, due to post-zygotic errors. Most of these embryos will die before developing to blastocysts; nevertheless, by then, more than 50% will still be affected by aneuploidy. Uniform aneuploidy occurs in 25% of blastocysts, but the mosaic form is still more common at 35%, with only 9% overall having more than a third of euploid cells. In the last decade, the application of comparative genomic hybridisation (CGH) has allowed the detection of partial aneuploidy due to chromosome breakage in both oocytes and embryos. CGH, carried out both by metaphase and genomic array analysis, suggests that 20% of cleavage embryos will be affected by segmental imbalance, but in the case of blastocysts, this figure will fall to 5% (Wells et al., pers. commun., and our unpublished data). However, in this issue, the article by Voit et al., based upon previous data from single nucleotide polymorphism (SNP) arrays, gives an incidence of 70% in cleavage embryos, a figure that many find hard to accept. Notably, the whole genome amplification methods employed differ between the CGH and the SNP approaches. The final review in the Embryonic and Prenatal subsection is by Lebedev and covers mosaic aneuploidy in early fetal losses with a detailed analysis of the causative mechanisms involved. By the consecutive application of FISH with probes for all chromosomes, mosaicism levels of between 48 and 94% were detected in non-cultured tissues from spontaneous abortion of 5–12 weeks' gestation. Most notable was the finding of mosaic monosomies, previously not seen in humans post implantation.

The final part of the section on Aneuploidy at Different Life Stages covers somatic aneuploidy. Reish et al. compare the occurrence of sporadic aneuploidy in trisomic individuals with that in a control group and find it to be significantly increased in the cells of those with constitutional aneuploidy. This finding accords with that of Perrin et al.; their investigation of DNA fragmentation in sperm shows an increased frequency in sperm with a chromosomal imbalance due to a constitutional anomaly.

Gisselson reviews the mechanisms of whole chromosome gains in tumour cells; besides being intrinsically interesting, this topic is also important for our understanding of events that occur during preimplantation embryo development.

Finally, Pinton et al. report on meiotic studies in a chromosomally mosaic boar.

The section on Genetic Regulation of Chromosome Segregation opens with an excellent overview by Homer on homologous disjunction in mouse and human oocytes, which points out the extraordinary similarities between the proteins mediating and regulating chromosome segregation during both meiosis and mitosis. Recent data from mouse models are discussed, which provide new insights into the progressive dysfunction of the spindle assembly checkpoint (SAC) system in age-related aneuploidy. The essential role of cohesin in the regulation of sister chromatid cohesion during meiosis is the subject of the two following chapters. Barbero analyses in detail the establishment, the maintenance and the removal of cohesion during chromosome segregation, and the relationship with aneuploidy. In addition, the unexplored role of cohesin defect in various human syndromes, known as cohesinopathies, is presented. Clift and Marston focus their contribution on the crucial role of shugoshin proteins in the stepwise loss of cohesion during meiosis. A large panel of experimental data from yeast, *Drosophila* and mammals is reviewed to explore the regulation function of shugoshin as well as the regulation of shugoshin. An important aspect of discussions on the fidelity of the division process is the synchronisa-

tion of chromosome segregation. Matos and Maiato review the complex interactions between microtubules and chromosomes in the synchronous progression of chromosomes through anaphase and the mechanisms ensuring the correction of chromosome attachment to the mitotic spindle.

The final section of this issue is devoted to Environment and Epigenetics, two critical aspects in the genesis of aneuploidy. Simple as it might seem, it is not yet clear how environmental aneugenic agents affect chromosome segregation. Pacchierotti and Eichenlaub-Ritter provide a comprehensive review on the principal agents and exposures that might directly affect chromosome segregation in both somatic and germinal cells. The role of epigenetic alterations and gene-environment interaction in the aetiology of human aneuploidy are addressed. Another significant aspect of the relationship between environment, epigenesis and aneuploidy is the occurrence of fertility problems. In their contribution, Ioannou and Griffin explore the correlation between male infertility and chromosome abnormalities, but they also stress how the nuclear organisation of chromosome territories could be correlated to male infertility. This third section closes with an overview on the always intriguing question of the potential effect of paternal age on aneuploidy occurrence. Gothami et al. give an excellent summary of the topic. They discuss the controversial results drawn from epidemiological surveys as well as gametic and molecular studies.

On the basis of these reviews, it is clear that much remains to be discovered about the genesis and the regulation of aneuploidy in humans. New insights into the mechanisms of chromosome segregation and aneuploidy occurrence will probably be gained with the rapid expansion of gene expression profiling. One can hope that the contributions united in this new themed issue of *Cytogenetic and Genome Research* will provide interesting suggestions for future research.

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