PREFACE

During the past few years, medical interest in mental retardation has progressively increased, more particularly after the development of clinical cytogenetics and genetic services. This has resulted in the delineation of an increasing number of new syndromes, a better management of the mentally retarded and accurate genetic counselling towards individuals and couples confronted with the occurrence of mental retardation in their family.

Chromosome abnormality is one of the major causes of mental retardation. Chromosome abnormality could be numerical or structural which could occur both in autosome and/or sex chromosome. More than 70% of all chromosomal errors are associated with early spontaneous abortions in humans and nearly one half of all those detected among new borns are aneuploids.

Aneuploidy is a condition in which an organism or a cell possesses fewer or more chromosomes than an exact multiple of the haploid number. Aneuploidy may result by fertilization of an aneuploid gamete, which in turn arises through a defect in the meiotic division. In man, the consequences of aneuploidy are severe and causes enormous human suffering and unhappiness.

Trisomy 21 is the most common and frequently identified numerical autosomal chromosome abnormality. Individuals born with this trisomy suffer from a characteristic spectrum of physical and mental problems. The high frequency and obvious clinical importance have combined to make this the most intensively studied of all human chromosomal abnormalities. The mechanism for origin of trisomy has remained an enigma. Although, much progress has been made, the mechanisms underlying non-disjunction in man remain largely unknown. The suggested causal
factors leading to non-disjunction include maternal age, genetic predisposition, interchromosomal effect and environmental factors such as viruses, mutagens, chemicals and radiation.

Several studies have presented data indicating that certain individuals or families have a tendency of producing aneuploid offspring. Moreover, it has been suggested that predisposition to meiotic aneuploidy could also be reflected in the mitotic cells. Therefore, the present study was undertaken to investigate some of the suggested etiological factors in causing non-disjunction. Cytogenetic analysis was also carried out in mentally retarded children with emphasis on Down Syndrome.

Down Syndrome was the major abnormality detected in the mentally retarded children investigated. The results obtained from acrocentric chromosome association study suggest that increased associations might be one of the factors for non-disjunction. Analysis of telomeric associations in Down Syndrome children revealed that significantly increased associations might predispose these children to leukaemia and premature ageing. Cytogenetic findings in parents of trisomy 21 children indicate an "interchromosomal effect" in the parents with inversions and variants. From the studies carried out on parental origin of extra chromosome 21 in Down Syndrome families, it could be concluded that maternal non-disjunction occurred in 83.8% cases and paternal non-disjunction in the remaining cases. Further, majority (80.9%) of the cases occurred due to error in the first meiotic division. The results obtained from the mitotic cell division errors in mothers of Down Syndrome showed that some of these women have a condition of cellular defect that can induce alterations in the basic mechanism controlling spindle microtubular polymerisation in their dividing cells. Analysis of spontaneous abortion rates in mothers of trisomy 21 and control mothers
indicate that the high frequency of fetal loss in young mothers of Down Syndrome might suggest a risk of having a live born aneuploid child.

The thesis has been organised in six chapters as under:

Chapter I: Introduction

Chapter II: Cytogenetic studies in mentally retarded individuals with special reference to Down Syndrome families. This chapter includes:

(A) Cytogenetic findings in mentally retarded patients.

(B) Cytogenetic findings in parents of free trisomy 21.

(C) Acrocentric chromosome association in Down Syndrome.

(D) Telomeric Association in Down Syndrome.

Chapter III: Parental origin of trisomy in Down Syndrome.

Chapter IV: Studies on mitotic cell division errors in relation to non-disjunction.

Chapter V: Spontaneous abortions in mothers of Down Syndrome.

Chapter VI: Summary and Conclusions.

PUBLICATIONS


2. Inherited maternal Robertsonian Translocation involving chromosome 21 and paternal pericentric inversion of chromosome 9 in a Down Syndrome child
3. 'De novo' duplication of 16q in a child with delayed development - case report (under preparation).

ABSTRACTS AND PRESENTATIONS


7. Singh Divya. Cytogenetic studies in Down Syndrome and observations on the possible origin of non-disjunction. ISCA Young Scientist Programme (in the Medical and Veterinary Section) 84th Indian Science Congress, Delhi University, Delhi, Jan. 3-8, 1997.


Indeed, more has probably been said & written in the last twenty years about the etiology of human aneuploidy, and yet less is probably known about this particular aspect of the problem than any other.

- Bond & Chandley