*Psychological Medicine*, 1982, **12**, 231–233
*Printed in Great Britain*

EDITORIAL

# Chromosome loss and senescence[1]

In most cytogenetic laboratories routine chromosome analyses are carried out on cultured, human lymphocytes. In the majority of individuals a number of these cells are aneuploid, i.e. they are missing, or have gained, one or more chromosomes. A correlation between the percentage of aneuploid cells and age was first shown by Jacobs *et al.* (1961).

Since then, a relationship between increased hypodiploidy (chromosome loss) and age in females has been confirmed by several laboratories (Jacobs *et al.* 1963; Hamerton *et al.* 1965; Sandberg *et al.* 1967; Cadotte & Fraser, 1970; Jarvik & Kato, 1970; Nielsen, 1970; Jarvik *et al.* 1974*b*; Martin *et al.* 1980). The evidence for a similar phenomenon occurring in males is less conclusive, although Martin *et al.* (1980) found that it does occur to a significant extent. The incidence of hyperdiploid cells (where extra chromosomes are present) is very low in both aged and young subjects but does increase slightly with age.

The human chromosome complement can be divided into 7 groups, based on the size and morphology of the chromosomes. Many workers in this field observed that, in females, an excessive number of cells were missing a chromosome from the C/X group and, in males, from the G/Y group. It was suggested that it was the sex chromosomes that were being lost. Although this has not been confirmed in males, the use of Giesma banding has established that one of the X-chromosomes is lost in females (Fitzgerald, 1975; Martin *et al.* 1980).

It appears that there is an overall increase in chromosome loss with age in females and possibly in males. In addition, there appears to be a second process operating in females involving one of the X-chromosomes. Jacobs *et al.* (1963) and Hamerton *et al.* (1965) observed that the incidence of hypodiploidy increased gradually with age in males. In females the pattern was similar until middle age, when the increase in hypodiploid cells underwent a sudden jump. The rate of increase levelled out again at 65–70 years. Martin *et al.* (1980) found that not only had hypodiploidy increased significantly in both sexes when compared with young subjects, but that the incidence in elderly females was also significantly greater than in elderly males. They suggested that this difference could be due to the excessive number of cells missing an X-chromosome in the ageing females.

Before ascertaining how age can cause an increase in hypodiploidy, the factors contributing to the existence of such cells in young subjects must be considered. The incidence of chromosome loss must depend, first, on the frequency of non-disjunction and, secondly, on the ability of the resulting abnormal cells to survive. Jarvik *et al.* (1974*b*) and Nicholls *et al.* (1978) observed that chromosome loss by group in young subjects does not follow a purely random pattern. Both authors also took into consideration the factor of chromosome size on the basis that the smaller the chromosome, the more likely it is to be lost during cell division. Two other factors could promote non-disjunction. Premature centromeric division (PCD) is a process which causes early separation of the centromere during mitosis. The chromatids orientate independently on the spindle; if both move to the same pole a hypodiploid and a hyperdiploid cell will result. A similar outcome will occur if, as suggested by Stadler *et al.* (1965), the presence of heterochromatic 'stickiness' physically delays chromatid separation during mitosis. Once non-disjunction has occurred, the continued existence of the aneuploid cells depends on their ability to survive.

Yunis (1965) considered that survival was dependent on the genetic importance of a chromosome to the cell as a whole. Thus a chromosome with a large amount of late-replicating DNA (which Yunis thought could be an expression of metabolic gene inactivation) would not affect cell survival if it were lost or present in excess. Hoehn (1975) used a similar concept in his construction of an

[1] Address for correspondence: Judith M. Martin, Department of Neuropathology, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF.

ideogram showing the relative genetic lengths of the chromosomes. The genetic length is the proportion of a chromosome that is genetically active: the greater the genetic length, the more important is the chromosome to cell survival. Nicholls *et al.* (1978) incorporated genetic length (as well as chromosome size) into their model for chromosome loss in young males and females. While the pattern of loss in these subjects conformed very well to the expected values calculated from this model, that of aged subjects was significantly different.

The next problem is how does ageing cause changes in the frequency of non-disjunction and cell survival. Orgel's error theory of ageing (Orgel, 1963, 1970) proposed that an accumulation of abnormal proteins could be caused by specific mutations in structural genes. Martin *et al.* (1980) suggested that such an accumulation of mutations in the appropriate genes could result in inaccurate control of mitosis and an increase in the frequency of non-disjunction – for example by PCD. Stadler *et al.* (1965) postulated that the heterochromatinization of autosomal segments could be under genetic control. A change in the distribution of heterochromatin may cause an increase in delayed chromatid separation and therefore in non-disjunction. In addition, since heterochromatin is generally considered to be genetically inactive, a change in the genetic length of a particular chromosome may decrease its influence on cell survival.

A mechanism for excessive sex chromosome loss was suggested by Hamerton *et al.* (1965). Since the Y-chromosome and one of the X-chromosomes are relatively genetically inactive, aneuploid cells associated with these chromosomes would be more likely to survive than if an autosome were involved. However, they give no explanation as to why this does not occur in young subjects. Fitzgerald (1975) did give such an explanation, at least in females. He found a higher incidence of PCD in women over 60 years than in young subjects. Using Giemsa banding he showed that the chromosome involved was an X-chromosome. The resulting cells had a chromosome complement of 45,X (72%), 47,XXX or with X-'fragments'. This led him to suggest that non-disjunction caused by PCD for some reason results mainly in hypodiploid cells.

Jarvik (1965) suggested the possibility that hypodiploidy may be more frequent in subjects with senile dementia than in aged controls. This was tested by Nielsen (1968, 1970). His results were negative in the males; however, in the females the senile dements (10 subjects) had a significantly greater frequency of chromosome loss than aged controls (10 subjects). Jarvik *et al.* (1971) tested 15 female controls and 8 senile dements with similar results. However, Jarvik *et al.* (1974*a*), using a larger number of subjects (42 controls and 36 senile dements), found that the difference in chromosome loss between the two groups failed to reach significance. They thought a possible reason for this was that, whereas their first group had been resident in the community, the second was taken from old peoples' homes. They also consider that the control group could have included subjects undergoing subtle mental changes, although they appeared physically and mentally normal. This, it was argued, would tend to increase artificially the frequency of hypodiploidy in the control group. However, Martin *et al.* (1981) could find no difference in hypodiploidy between 55 elderly female controls and 46 senile dements. The source of subjects in this survey was similar to that of Nielsen's (long-stay geriatric, surgical and neurological wards and an old peoples' home). Both Jarvik *et al.* (1974*a*) and Martin *et al.* (1981) noted a high degree of individual variation in hypodiploidy, an observation that would make it essential for a suitably large sample to be used in such a survey.

Chromosome loss appears to be influenced only by ageing in general. However, a fruitful line of research could be an investigation into hypodiploidy in patients with pre-senile dementia who are still in their middle age. Two recent papers have been published which show encouraging results with patients with Alzheimer's disease. Both Ward *et al.* (1979) and Nordenson *et al.* (1980) found that most of their Alzheimer patients had a higher degree of hypodiploidy than age- and sex-matched controls.

In conclusion, let us consider some of the implications of increased chromosome loss and ageing. Jarvik *et al.* (1974*a*) suggested that increased hypodiploidy could serve a beneficial purpose: those who have a high frequency of these cells in early life are somehow selected for survival. However, what must be borne in mind is that all the studies on chromosome loss and ageing mentioned in this review have utilized lymphocytes. This would suggest that hypodiploidy could have a

detrimental effect on the immune response of an individual. There is evidence that both the immune response and the ability to respond to mitogenic agents (such as phytohaemagglutinin) does decrease with age (Pisciotta *et al.* 1967; Roberts-Thomson *et al.* 1974). The reason for excessive X-chromosome loss in females remains a problem. Jacobs *et al.* (1963) suggested that, as they observed this increased loss to begin between 45 and 65 years, it was in some way associated with hormonal changes occurring at this time.

Obviously, although much progress has been made in the problem of chromosome loss and ageing, many questions still remain unanswered, relating both to the causes of hypodiploidy and its implications to the persons in which it occurs. It is hoped that future research – cytogenetic, biochemical and physiological – will answer these questions.

JUDITH M. MARTIN

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