33. Aneuploidy in Human Lymphocytes in Extreme Old Age

The Relationship between Natural and Artefactual Aneuploidy

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Introduction. At present it is generally believed that aging is accompanied by an increase in the numbers of cells with altered chromosome sets.\(^1\)\(^-\)\(^6\) However, the problem of aneuploidy in extreme old age (80 years or more) has hardly been subjected to the systematic investigation.

The purpose of this study was to examine quantitative chromosome changes and the relationship between artefactual and natural aneuploidy in subjects 80 to 114 years of age using karyotype analyses.

Materials and methods. Chromosomes were studied in 1136 karyotypes of relatively round metaphases from 40 lymphocyte cultures. Peripheral blood lymphocytes were taken from 40 apparently normal subjects aged 80 to 114, including 26 men (729 karyotypes) and 14 women (407 karyotypes). 963 karyotypes from 48 donors (23 women and 25 men) aged 20 to 48 were served as the control. Cultivation of lymphocytes was during 72 hours.

Results. Our experimental data, as summarized in Table I, show that the numbers of cells with 45 and 47 chromosomes and the total frequency of aneuploidy are considerably increased at the age of 80 to 114 years. This observation is supported by most published data\(^1\)\(^-\)\(^1\)\(^1\) and seems to indicate that the factors contributing to the frequent appearance of cells with a hypo- or hyperdiploid chromosome set are specific for senescence. However, the relationship between natural and artefactual aneuploidy in old age has not been investigated to date. Yet this problem is of considerable theoretical and practical importance. From the practical point of view it can be formulated as follows: are the quantitative changes in karyotype to be regarded as normal for old age or as different manifestations of some abnormality?

For studying the relationship between natural and artefactual aneuploidy, the probability of natural aneuploidy was higher among senile women as compared with the control. Our results indicated that the probability of natural aneuploidy rose substantially in the group of elderly women and that of artefactual aneuploidy was increased among elderly men. The problem of natural aneuploidy in men remained unclear.

An analysis of the distribution of missing and additional chromosomes in karyotypes from subjects aged 20 to 48 and 80 to 114 showed that old age in both sexes was associated with considerably larger losses of chromosomes of groups A and B. At the same time in senile men the numbers of additional chromosomes of group G were increased.

At the age of 80 to 114 the proportion of polyploid cells was 0.96% (vs
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0.40% in the control group), including 0.61% (vs 0.20%) of cells with endoreduplicated chromosomes.

Discussion. In 1961 Jacobs et al.\(^1\) first described the age-related deviations from the diploid chromosome count in somatic cells from normal subjects: the numbers of aneuploid cells increased with age from 5.21% (at 25 to 34 years) to 13.7% (above 65 years). The authors believed that, apart from artefactual aneuploidy, this increase was determined to a certain extent by the age factor.

The findings of Jacobs et al. were confirmed subsequently by many reports on age-dependent variability of chromosome sets in somatic cells.\(^2\)\(-\)\(^{11}\) Our results concur with these observations.

Practically in all of the above-mentioned studies the higher frequency of aneuploidy in old age was attributed to the hypodiploidization. The fragility of lymphocytes was shown to increase with senescence,\(^12\) and this phenomenon could lead to the appearance of hypodiploid cells (due to damage of lymphocytes during preparation). In such a case it would be logical to expect a loss of chromosomes located at the periphery of the nucleus. Since the peripheral location is usually a feature of late replicating chromosomes: X and Y, 4\(-\)5, 13, 18, 21\(-\)22,\(^13\)-\(^{17}\) the numbers of cells lacking these chromosomes would increase with age. Indeed, such a tendency was noted by many investigators for X-Chromosome,\(^9\),\(^11\),\(^16\),\(^19\),\(^20\) 21\(-\)22nd and Y-Chromosome\(^1\)-\(^{31}\),\(^5\),\(^10\),\(^21\) and chromosomes of group E.\(^22\) We observed a rise in the percentage of metaphases with missing chromosomes of groups A and B.

However, we are inclined to agree with Kerkis et al.,\(^12\) who believe that the age-dependent increase in lymphocyte fragility is but a manifestation of some general changes occurring in the cells of a senescent host, which result in the hyperviscosity of the cytoplasm and thereby contribute to abnormal disjunction of chromosomes.

It should be noted that the senescence is accompanied by an increase in the numbers of chromosomes with premature disjunction of the centromere\(^11\),\(^18\),\(^19\) and that the nondisjunction of material chromosomes leading to abnormal embryogenesis becomes more frequent with age.\(^23\),\(^24\) These facts seem to indicate that the process of aging results in the appearance of endogenous factors which cause a loss of certain chromosomes to an extent depending, probably, on the age and sex of the subjects selected for study.\(^6\)

In the present investigation we attempted to define the relative contributions
of natural and artefactual aneuploidy to the total aneuploidy observed in senile subjects of both sexes. Our results show that the probability of the artefactual aneuploidy among elderly men is higher than in the control group. A similar conclusion is suggested by other studies. The increase in the artefactual aneuploidy in the group of old men may probably be attributed to a selective loss of chromosomes (E-G, Y) predetermined by their sizes and location in the cell nucleus.

In our group of senile women the probability of artefactual aneuploidy was lowered (T = -1.40), while that of the natural aneuploidy rose considerably (T = 2.10). Our analysis of the data published by Mattevi and Salzano for girls aged 10 to 13 and women of 64 to 96 years also indicates a substantial increase in the natural aneuploidy in the latter group.

As compared to control, the proportion of polyploid (including endoreduplicated) cells was elevated in both sexes at the age of 80 or more. This observation confirms previous findings. The age-related increase in polyploid cells is probably caused by hormonal shifts occurring during senescence.

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**References**

12) Kerkis, Y. Y. et al. (1967): Genetika (USSR), 4, 137–141.