# NOTES AND COMMENTS

## MOSAICISM IN MAN, INVOLVING THE AUTOSOME ASSOCIATED WITH MONGOLISM

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Examples of chromosome mosaicism, that is, the presence in one individual of cells with different chromosome constitutions, have been described recently in man. Ford *et al.* (1959*b*) and Hayward (1960) both found XXY and XX cells in males diagnosed as Klinefelter syndrome. Ford (1960) reported the finding of XO and XX cells in females diagnosed as Turner's syndrome, and Jacobs *et al.* (1960) found XXX and XO cells in a female with primary amenorrhœa. Blank *et al.* (1960) and Hirschhorn *et al.* (1960) both found XY and XO cells in subjects with evidence of hermaphroditism. All of these examples involved the sex chromosomes only, and otherwise showed a normal complement of 22 pairs of autosomes. An autosomal mosaic has recently been described by Clarke *et al.* (1961) who found normal cells and cells which were trisomic for chromosome 21 in a mongoloid child.

Böök *et al.* (1959), Ford *et al.* (1959*a*), Lejeune *et al.* (1959) and Jacobs *et al.* (1959) found that mongolian idiots all have a small acrocentric chromosome additional to the normal complement. This chromosome is generally agreed to be number 21 in the Denver classification (*Lancet*, 1960 (i), 1063). The trisomy of this chromosome, causing mongolism, probably has its origin, in most cases, from primary non-disjunction during oögenesis (Jacobs *et al.*, 1959) forming an egg cell with two chromosomes 21, which is fertilised by a normal sperm.

The present report is of a case of mosaicism involving autosome 21, which is unique in showing three different complements of this chromosome.

### 1. CASE REPORT

The subject, a 51 year old male, has always been regarded as a mongol, although he shows some atypical mongoloid traits. His stature is short. The back of his head is flat; the eyes, which are widely separated by a broad nasal bridge, do not have epicanthal folds or the typical mongoloid slant; the ears are large, but of normal shape and the tongue is of normal size. His chest is flat rather than rounded; there is no clinical evidence of congenital heart defects. The hands and feet are short and broad; the left hand shows a " simian crease ", but the creases of the right hand and the feet are normal. The subject shows a very severe grade of mental deficiency and is unable to speak or to obey simple instructions, although he can feed himself. His mother was 38 years of age at the time of his birth.

## 2. METHODS

Leucocytes from peripheral blood were cultured, treated with colchicine and hypotonic saline by a modified form of the method of Moorhead *et al.* (1960). The cells were spread by air drying, stained with a May-Grunwald, Giemsa combination and mounted in *Depex*. This technique gives many well spread mitotic figures with a minimum of damage or chromosome loss, and allows accurate counting and identification of the chromosomes.

## 3. CHROMOSOME STUDIES

The chromosomes were counted in 101 well spread and undamaged cells with the following results :

| Chromosome number . . | 41 - 46 | 47 | 48 | Total |
|---|---|---|---|---|
| Number of cells . . . | 1 | 42 | 53 | 5 | 101 |

These results contrasted sharply with those from other chromosome studies we have made by the same method, all of which showed a single modal number with little variation from it. Twenty-nine cells with 46 chromosomes, 39 cells with 47 chromosomes and 3 cells with 47 chromosomes were analysed in detail with special regard for the number of small acrocentric chromosomes present. A normal male shows 5 of these chromosomes : 2 of number 21, 2 of number 22 and the Y chromosome. The cells with 46 chromosomes all contained 5 small acrocentric chromosomes, those with 47 chromosomes all contained 6 small acrocentric chromosomes, and the 3 cells with 48 chromosomes all showed 7 small acrocentric chromosomes.

These results clearly indicate mosaicism for one of the small acrocentric chromosomes, and the mongoloid facies of the subject is strong evidence that this is chromosome 21.

## 4. DISCUSSION

Mosaicism in an individual will result from secondary non-disjunction of a chromosome in a post-zygotic mitosis. The present triple stem-line mosaic is not likely the result of non-disjunction of chromosome 21 during the divisions of a normally constituted zygote with 46 chromosomes, because if this occurred during the first cleavage division, 45 and 47 chromosome stem-lines would result, and if during the second or later cleavage divisions, 45, 46 and 47 chromosome stem-lines would result. Assuming a zygote which is trisomic for chromosome 21, that is a " mongoloid zygote ", non-disjunction of chromosome 21 in the first cleavage division would give 46 and 48 chromosome stem-lines, whereas non-disjunction in the second or a later cleavage division would give stem-lines with 46, 47 and 48 chromosomes, as were observed. It is most probable therefore that the present mosaic is the result of non-disjunction of chromosome 21 in the second or a later cleavage division of a zygote which was trisomic for this chromosome because of an earlier non-disjunction during gametogenesis. The high frequency of cells with 47 chromosomes supports this view, because non-disjunction of chromosome 21 in one of the cells during the second cleavage division, for instance, would produce a 4-cell stage made up of two cells with 47 chromosomes one cell with 46 chromosomes and one cell with 48

chromosomes. However, such a ratio of different stem-lines might not be maintained in consequent divisions, and Ford *et al.* (1959*b*) consider that stem-lines which are nearer normality may have a selective advantage. Such a view accords with the increase in frequency of the normal 46 chromosome stem-line relative to the abnormal 47 chromosome one, and the decrease in frequency of the more abnormal 48 chromosome stem-line observed in the present mosaic.

Ford *et al.* (1959*b*), Ford (1960) and Hayward (1960), postulate similar origins for the XXY/XX and XO/XX mosaics, that is, mitotic non-disjunction in the second or later cleavage divisions of abnormal XXY and XO zygotes. Hayward considers that the presence of an unbalanced genotype, as in the XXY Klinefelter syndrome, might make mitotic non-disjunction more likely. If these mosaics arose in this way, other stem-lines must have been produced as a result of the secondary non-disjunction. Cells with 44 autosomes and no sex chromosomes in the Turner's mosaics presumably would not have been viable. A 48 chromosome stem-line with the XXYY constitution would have been produced in the Klinefelter mosaic, but neither Ford nor Hayward found evidence of it. Its absence may be surprising, for this chromosome constitution is by no means inviable as is seen from the report (Muldal *et al.*, 1960) of a case of Klinefelter syndrome with the XXYY genotype. However, it is possible that the 48 chromosome stem-line was at some selective disadvantage and was either eliminated or present at too low a frequency to be included in the samples studied. Ford *et al.* (1959*b*) outline evidence that mammalian cells with different visible chromosome constitutions reproduce at different rates, and that cells with a normal chromosome constitution have a selective advantage. Another factor which may explain the failure to find the 48 chromosome stem-line is illustrated by the different chromosome analyses obtained from different tissues of the XXX/XO mosaic by Jacobs *et al.* (1960). Cultures of leucocytes and skin cells showed modal stem-lines of 45 and 47 chromosomes, whereas cultures of sternal marrow contained only cells with 45 chromosomes. They consider this is likely due to the marrow consisting only of cells with 45 chromosomes, whereas the lymph nodes and other sites in the reticulo-endothelial system may contain cells of the other type. Chromosome preparations from bone marrow cells only were examined in both of the Klinefelter mosaics.

Jacobs *et al.* (1960) consider that the most likely explanation of the XXX/XO mosaic is non-disjunction of the X chromosomes during the first cleavage division in a normally constituted XX zygote. The XY/XO mosaics of Blank *et al.* (1960) and Hirschhorn *et al.* (1960) are presumably due to loss, or non-disjunction, of a Y chromosome in an early cleavage division of a normal XY zygote. The 61 per cent. and 41 per cent. frequencies of the 45 chromosome XO stem-line observed in these mosaics are difficult to reconcile with the view of a selective advantage of cells with the normal chromosome constitution.

Stern (1960) has recently reported a mosaic, in *Drosophila*, which like the present mosaic consisted of three types of cells. It is believed that non-disjunction of the X chromosomes, in an early cleavage mitosis of an XX zygote, produced stem-lines having X, XX and XXX constitutions. Non-disjunction occurred during a later cleavage division than in the case of Jacobs *et al.* (1960).

## 5. SUMMARY

The cells from a leucocyte culture of a man presenting mongoloid features showed distinct stem-lines of 46, 47 and 48 chromosomes, which were considered to be disomic, trisomic and tetrasomic respectively for chromosome 21. This mosaicism probably resulted from mitotic non-disjunction of chromosome 21 in the second or a later cleavage mitosis of a zygote which was already trisomic for this chromosome.

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