Distributive Pairing and Aneuploidy in Man

Abstract. *The extrapolation of the "distributive-pairing hypothesis" of meiosis in* Drosophila melanogaster *females to human gametogenesis is proposed to account for the co-occurrence of rare karyotype abnormalities in human families. A description of the hypothesis is presented with its application to some established cases in the cytogenetic literature.*

The co-occurrence within single human kinships of various kinds of rare karyotype abnormalities, such as aneuploidy for an autosome associated with a translocation between unrelated autosomes (*1–4*), aneuploidy for the sex chromosomes associated with autosomal translocations (*5–6*), or aneuploidy for the sex chromosomes associated with aneuploidy for an autosome (*7–10*), has led several authors to suggest that these events are not fortuitous (*2, 3, 6, 8*). However, a general mechanism which could account for a causal relationship between them has not been advanced. In the female of *Drosophila melanogaster* the coincidence of some of the same kinds of events has been known for many years (*11*), the interdependence between them has been found to be nonhomologous pairing (*12*), and the principles underlying chromosome behavior at this time have recently been elucidated and incorporated into the "distributive-pairing" theory of meiosis (*13*).

The meiotic picture that has emerged in *Drosophila* discloses that homologous pairing (that is, highly specific pairing necessary for exchange) occurs first and is followed by a second type of pairing, *distributive pairing*, which determines segregation. Chromosomes that have undergone exchange, and are presumably physically joined by a chiasma, disjoin regularly and have no opportunity for involvement with a heterolog (nonhomolog). Chromosomes that have not undergone exchange make up a pool whose members may pair homologously or nonhomologously or not at all, depending on the composition of the pool. If only one chromosome is present, it will assort randomly; if two homologs constitute the pool, they will pair and disjoin regularly; if at least two heterologs are present in the pool, the possibility of nonhomologous association followed by nondisjunction of homologs and the production of aneuploid types exists. Recent findings (*14*) disclose that the pairing preferences exhibited at this time are a function of similarity in chromosome length.

The role of heterozygous chromosomal rearrangements, such as inversions and translocations, is to increase the contribution of nonexchange chromosomes to the distributive pool by decreasing the probability of exchange. In the case of inversions, the effectiveness of any particular inversion system is correlated with its size, its position, its complexity, in short its ability to interfere with crossing over between homologs. In *Drosophila*, a single, heterozygous, paracentric inversion, in an X chromosome, can increase the noncrossover X bivalents from about 5 percent to about 70 percent, with, of course, a concomitant increase in the presence of both X's in the distributive pool. In man, paracentric inversions, as well as many kinds of pericentric inversions are not detectable in mitotic chromosomes. Koller (*15*), however, has presented evidence for the presence of an inverted sequence in primary spermatocytes. It is possible that such inversions are playing a major, but as yet undetected, role in the production of aneuploid types. Similarly, heterozygous reciprocal translocations, particularly those in which one chromosome is very small and thus unlikely to undergo exchange with either of its normal homologs, will contribute a member to the pool with a very high frequency. Translocations have been observed in human karyotypes and it was their presence in a family showing an unrelated kind of aneuploidy (*1*) that first suggested to us that the distributive pairing hypothesis might be extended to man. Finally, in the *Drosophila* female, a supernumary Y chromosome or a small duplicated chromosome practically never undergoes exchange and hence is very effective in increasing nondisjunction of any heterolog in the pool. An extra Y has been detected in the human male (*7*), the evidence suggests it does not undergo exchange (*16*) and that it, too, is effective in causing autosomal nondisjunction (*7*).

Once an aberration is present in the genome, its ability to interfere with the disjunction of a heterologous chromosome will depend on its simultaneous presence in the pool. This must, in turn, depend on the exchange frequency of the heterologous pair. If certain chromosomes are noncrossovers more often than others, they will be members of the distributive pool more often and should occur as aneuploids more often. In general the frequency of exchange between homologs shows a positive correlation with chromosome length. For instance, in *Drosophila melanogaster*, less than two percent of chromosomes 2 and 3, which are the longest members of the genome, are noncrossovers, about 5 percent of the somewhat smaller X chromosomes are noncrossovers, whereas chromosome 4, which is extremely small, is always a noncrossover. Therman *et al.* (*8*) have noted that for the three types of autosomal aneuploidy recognized in humans, that is Down's syndrome (mongolism), the E syndrome and the D syndrome, the frequency of each in the population is related to the length of the chromosome involved. This observation led Therman *et al.* (*8*) to suggest, as one possibility, that the probability of nondisjunction decreases steeply with increasing chromosome length. In terms of the hypothesis being presented, the link between length and nondisjunction is the probability of exchange. Lastly, it is evident that the presence of a second aberration involving another chromosome of the genome can alter the incidence of heterologs in the pool from a possibility to a virtual certainty.

Extension of the distributive pairing hypothesis to human gametogenesis provides a satisfactory explanation for a number of puzzling cases described in the cytogenetic literature. A few such interpretations are presented here. Moorhead *et al.* (*1*) have reported a phenotypically normal woman whose karyotype of 45 chromosomes includes a translocation between chromosomes 13 and 22 which is recognizable as a large metacentric corresponding to those in group C (*6–12*). The reciprocal small chromosome of the translocation was not found in her leucocytes. Her progeny consisted of four severely retarded mute children, each possessing 45 chromosomes and including the large translocation metacentric, one child with 47 chromosomes showing regular trisomy for chromosome 21 and lacking the translocation metacentric, and one normal child. The authors have considered that the translocation may have been involved in the production of the mongoloid. According to the interpretation proposed here, trisomy for chromosome

21 arose through the presence in the distributive pool of the undetected part of the translocation. If the chromosome is very small, as the size of its reciprocal part suggests, the probability of exchange between it and its normal homologs is negligible, and its presence in the pool is virtually assured. When chromosomes 21 fail to undergo exchange, and this may not be a rare event, they too will be present in the pool. Nonhomologous pairing between the small translocation chromosome and one or both 21 chromosomes will often result in the presence of two 21 chromosomes in a gamete from which the translocation is absent. The grounds for assuming that the mother is a mosaic for the small translocation chromosome rests on the normal phenotype she displays, and the abnormal phenotype but identical karyotypes of four of her offspring. Since the four similarly affected sibs carry only the large chromosome of the translocation the absence of the reciprocal part could be responsible for their phenotypic abnormality. Furthermore, Penrose *et al.* (*17*) have observed that a complete translocation may be present in the gonial cells but absent in some of the somatic cells of an individual.

Recently, Hamerton *et al.* (*2*) have reported a case similar to that just described except for the fact that the translocation present in the mother of the mongoloid involves two large nonhomologous acrocentrics of the D group rather than a large and small acrocentric. The mother possesses a normal phenotype but her karyotype shows 45 chromosomes including a large metacentric resembling No. 3 and only four chromosomes of the 13–15 group, again suggesting mosaicism for the small translocation chromosome. The mother's sibship tends to substantiate this view for among ten sibs, five died in the first year of life (1 to 8 months) fitting expectation precisely if the small translocation chromosome were assorting randomly to produce duplication and deficiency gametes 50 percent of the time. Again it is assumed that the small translocation chromosome in the mother's germinal cells paired with chromosome 21 to produce a gamete carrying two 21 chromosomes and lacking the translocation.

A second category of abnormalities involves autosomal translocation associated with aneuploidy for the sex chromosomes. Several cases of this kind have been described by Lejeune (*5*, *6*). In one such case, a mother and her X0 daughter both carry a translocation between chromosomes 2 and 22. Here it may be postulated that one of the translocation chromosomes has paired with an X during oogenesis to cause X nondisjunction and the production of a gamete lacking both X's but carrying the translocation.

Aneuploidy for the sex chromosomes and autosomes comprise a third category. Hauschka *et al.* (*7*) have reported a case of 21 trisomy in which the father carries 47 chromosomes including two Y's. Besides the mongoloid, two abortions, a blue baby who died at 3 days, and an individual presumably mosaic for the sex chromosomes were reported. It is assumed the gamete giving rise to the mongoloid arose from pairing between the extra Y and chromosome 21 to produce a sperm carrying both 21 chromosomes and an X. Other abnormalities in the sibship could conceivably be traced to associations of a sex chromosome and nonrecombinant autosome.

A case reported by Therman *et al.* (*8*) shows D trisomy in one sister and Turner's syndrome in another. The authors point out that the incidence of each aneuploid type is rare enough to rule out coincidence. If a heterozygous inversion is postulated to be present in a pair of D chromosomes of one parent thus reducing exchange between these chromosomes, and should the sex chromosome also be present in the distributive pool, association between a sex chromosome and a D chromosome with random assortment of the other two members could lead to the formation of both the XDD and the nullo-XD gametes.

A number of cases in the literature report the appearance of Turner's or Kleinfelter's syndrome and mongolism in two sibs (*9*). These types might be expected if the mechanism which ensures regular segregation of the sex chromosomes in the male were to break down. Since exchange probably does not occur between the X and Y (*16*) the function of the sex vesicle (a Feulgen-positive structure seen at pachytene that contains the X and Y) may well be, as has been suggested by Valencia (*18*), to ensure the isolation of the nonrecombinant sex chromosomes from any nonrecombinant autosomes. Should this system be defective, perhaps through failure to include the X and Y in a common vesicle or by precocious disappearance of the sex vesicle, the sex chromosomes would become available for heterologous associations. If this occurred in conjunction with a low exchange frequency between chromosomes 21, mongolism and aneuploid sex types could result.

Finally it is pertinent to note the extremely high frequency of familial chromosome abnormalities in an unselected group of mongoloids recently reported by Dekaban *et al.* (*3*) which led them to suggest that such " 'minor' abnormalities may increase the frequency of nondisjunction of other chromosomes during meiosis."

The "distributive-pairing hypothesis" has been carefully tested in *Drosophila*. Its application to human gametogenesis, although admittedly speculative, does provide a reasonable genetic explanation for hitherto anomalous events.

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References and Notes

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