

Theoretical bases for karyotype evolution.

II. The fusion burst in man and mouse

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ABSTRACT

As a theoretical standard for evaluating the high incidence of centric fusion in man and mouse, the relative probabilities of occurrence of reciprocal translocation (Tr), inversion (In) and centric fusion (Fu) were estimated based on the random-contact-and-exchange model. It was shown by this model that centric fusion was extremely rare ($Fu=0.0002$, $In=0.0521$ and $Tr=0.9477$ for a human haploid karyotype). On the other hand, the occurrence rate of centric fusion in human newborn babies and European feral mice was about 500–1,000 times higher than the theoretically expected values, which is termed here the "fusion burst". We suggest that the fusion burst may be induced by the physical proximity of telomeres on the nuclear membrane, and the exchange of DNA strands by errors of telomere replication mechanisms. The cytogenetical significance of the fusion burst is discussed with regard to the minimum interaction hypothesis proposed by Imai et al. (1986). We suggest two closely linked possibilities that (1) the fusion burst in man and mouse can theoretically be placed in karyotype evolution as a transitional phase in the main stream of the fission-inversion cycle, and (2) it may be accelerated by some unknown (mutagenic) factors other than ionizing radiation.

1. INTRODUCTION

Centric fusion has long been considered to be one of the major chromosomal mutations in animal karyotype evolution (White, 1954; 1973). The overwhelmingly abundant appearance of centric fusion in man (e.g., Borgaonkar, 1984) and mouse (Gropp et al., 1972; Capanna et al., 1976) seems to provide the most strong supporting evidence for the fusion hypothesis. In spite of such unilateral acceptance for fusion in the main stream in cytogenetics and given that directionality is

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very difficult to demonstrate in many cases, Todd (1970, 1975) and Imai (1978) have independently developed an alternative, i.e., the fission hypothesis. The fission hypothesis proposed by Imai is based on the non-random distribution of centromere localization on mammalian chromosomes (Imai, 1975; 1976), and on a series of theoretical analyses for the evidence (Imai, 1978; Imai and Maruyama, 1978; Imai and Crozier, 1980).

More recently, an attempt was made to reconcile the fusion-fission controversy by the *minimum interaction hypothesis* (Imai, 1986; Imai et al., 1986). This latter hypothesis predicts that karyotypes of eukaryotes evolve toward reducing the genetic risk resulting from reciprocal translocation, and the modes of karyotype evolution are framed mostly by the balance between nuclear volume at pachytene and genome size. If the ratio of genome size to nuclear volume is high, chromosomes will interact frequently, and thus the probability of occurrence of reciprocal translocation will increase. Monte Carlo simulation experiments (Imai et al., 1986) revealed that such a phenomenon is theoretically possible under the "hammock structure" (=suspension arch structure; a non-random chromosomal configuration at pachytene resulting from bonding the ends of bivalents to the nuclear membrane).

Centric fission is, in the minimum interaction hypothesis, recognized as one avoidance mechanism of the risk due to translocation, because the chance of chromosomal interaction decreases under the hammock structure as chromosome number increases by centric fission. In contrast, centric fusion seems to be evolutionarily less adaptive, because genetic risks would increase as the chromosome number is reduced by fusion. With this argument centric fusion would contribute, therefore, to karyotype evolution only as a local or temporal inverse current in the main stream of centric fission. For detailed discussions of the fusion-fission controversy, see Imai (1988). If this theoretical process reflects reality, it is reasonable to ask why fusions have overwhelmingly been observed in some animals (especially in man and mouse). This question is addressed in the present study.

2. ANALYSES AND DISCUSSION

1) *Stochastic analyses of human chromosomal aberrations*

In the present study human cells are classified into three categories (germ cell, somatic cell, and cancer cell). The relative frequencies of reciprocal translocation (Tr), inversion (In), and centric fusion (Fu) were compared among newborn babies, atomic bomb survivors in Hiroshima and Nagasaki, and cancer patients.

As is summarized in Tables 1 and 2, reciprocal translocation is the most dominant, and inversion the least frequent in the three rearrangements. However, the frequency of centric fusion is quite different between newborns and the other two categories, i.e., extraordinarily high in the former, but zero or almost

Table 1. The probabilities of occurrence of structural chromosomal mutations in human diploid karyotype (2K) and their frequencies in X-ray irradiated human skin cells, atomic-bomb survivors in Hiroshima and Nagasaki, and in human cancers

Type of chromosomal mutations	Theoretical expectation (2K)	X-ray irradiated human skin cultured cell*	Atomic-bomb survivors in Hiroshima and Nagasaki**	Human cancers***
Reciprocal translocation (Tr)	Tr (2K) 0.9738	0.9509 (600)	0.8689 (6754)	0.9431 (2256)
Inversion (In)	In (2K) 0.0260	0.0491 (31)	0.1311 (1019)	0.0489 (117)
Centric fusion (=Robertsonian translocation) (Fu)	Fu (2K) 0.0002	0.0000 (0)	0.0000 (0)	0.0079 (19)

* Savage and Bigger (1978).

** Data were supplied by Honda.

*** Mitelman (1985). To minimize the bias introduced by over-reporting specific common translocations, the following three translocations t(9;22), t(15;17) and t(8;21) were eliminated from the estimates.

zero in the latter two. The low incidence of centric fusion in radiation induced aberrations was pointed out by Searle (1975), and also observed in X-ray irradiated human skin cells (Savage and Bigger, 1978; Table 1), suggesting a general characteristic of chromosomal mutations induced by ionizing radiation. The question remains as to why so many fusions appear in newborns (Table 2). To answer this question in a quantitative sense, a theoretical standard for the frequencies of structural chromosomal mutations is required.

a) *Relative occurrence rate of chromosomal mutations under the random-contact-and-exchange model*

The random-contact-and-exchange model is herein used as the theoretical standard for expected chromosome rearrangements (for details see Imai et al., 1986). The probability of occurrence of inversion (In), centric fusion (Fu), and reciprocal translocation (Tr) in a haploid karyotype (K) is given by

$$\text{In}(K) = \sum_{i=1}^n C_i^2 \quad 1$$

$$\text{Fu}(K) = \left(\sum_{i=1}^{n'} S_i' \right)^2 - \sum_{i=1}^{n'} (S_i')^2 \quad 2$$

and

$$\text{Tr}(K) = 1 - \text{In}(K) - \text{Fu}(K) \quad 3$$

where C_i is the size of chromosome i , $\sum_{i=1}^n C_i = 1$ n is haploid chromosome number, and n' and S_i' mean the number and size of short arms of acrocentrics.

Table 2. *Theoretical expectations of frequencies of structural chromosomal mutations in man, and those observed in human newborn babies and in spontaneous abortions*

Type of chromosomal mutations	Theoretical expectations			Experimental data in newborn babies				
	A	B	C	D	E*	F**	G	H
	Probability of occurrence of chromosomal mutations in human haploid karyotype (K)	Frequencies of balanced type chromosomal mutations at fertilization	Frequencies of chromosomal mutations in newborn population	<i>de novo</i>	From parent	Total	From the table by Hook & Hamerton (1977)	Frequencies of chromosomal mutations in spontaneous abortions***
Reciprocal translocation (Tr)	Tr (K) 0.9477	Tr (f) 0.8192 } 0.9004	Tr (nb) 0.8344	Tr (NBdn) 0.7857 (10)	Tr (NBp) 0.3544 (28)	Tr (NB) 0.4130 (38)	0.4508 (55)	Tr (SA) 0.3095 (13)
Inversion (In)	In (K) 0.0521	In (f) 0.0992 } 0.1799	In (nb) 0.1650	In (NBdn) 0.0000 (0)	In (NBp) 0.1646 (13)	In (NB) 0.1413 (13)	0.0738 (9)	In (SA) 0.0238 (1)
Centric fusion (Fu)	Fu (K) 0.0002	Fu (f) 0.0001 } 0.0004	Fu (nb) 0.0006	Fu (NBdn) 0.2143 (3)	Fu (NBp) 0.4810 (38)	Fu (NB) 0.4457 (41)	0.4754 (58)	Fu (SA) 0.6667 (28)

* Actually means inherited from a carrier parent.

** Total of D and E.

*** Based on the data by Lauritsen *et al.* (1972), Creasy *et al.* (1976), Geisler and Kleinebrecht (1978), Kajii *et al.* (1980), and Hassold *et al.* (1980).

Formulas 1-3 are applicable to diploid karyotype (2K), where $\sum_{i=1}^{2n} C_i = 1$ and we use terms In(2K), Fu(2K) and Tr(2K).

The size of chromosomes was estimated based on 10 well spread metaphases obtained from cultured lymphatic cells of 5 males and 5 females (chromosomal preparations by T. H.). The photo cut-out technique (Wurster et al., 1971), i.e., the weight method (Imai, 1975), was used. Imai et al. (1986) utilized the conventional length method based on the data of the Paris Conference (Hamerton et al., 1972; Index D), but this was not used in the present study, because the size of acrocentric short arms is overestimated (ca. twice) by the length method (also see Imai, 1973). An identical result was obtained also by the area method (Oishi and Tonomura, 1966). The theoretically expected values are (in terms of the weight method) Tr(K)=0.9477, In(K)=0.0521, and Fu(K)=0.0002 for a haploid karyotype, and Tr(2K)=0.9738, In(2K)=0.0260, and Fu(2K)=0.0002 for a diploid karyotype. Our estimations indicate that centric fusion is negligibly rare under the random-contact-and-exchange model.

b) *Patterns of chromosomal mutations in irradiation experiments and human cancers*

It is a noteworthy finding that the pattern of radiation induced chromosomal mutations is very similar to that predicted theoretically under the random-contact-and-exchange model (Table 1). The data of X-ray irradiated skin cells by Savage and Bigger (1978) are Tr=0.9509, In=0.0491 and Fu=0. The same tendency was also observed in atomic bomb survivors of Hiroshima and Nagasaki (Table 1), though the relative frequency of reciprocal translocation is about 10% lower (Tr=0.8689) than the theoretical expectation (Tr(2K)=0.9738). The reduction in the incidence of translocation in these data may be the result partly of a non-random configuration of interphase chromosomes, and partly due to the instability of some translocations. We used in the present calculations chromosomal data of 1968-1975 for the Hiroshima population and of 1971-1978 for the Nagasaki population. Cells bearing unstable translocations would be eliminated preferentially during the 20-30 years after exposure to ionizing radiation.

As is discussed in a later section, X-ray induced chromosomal mutations in mouse sperm are Tr=0.98, In=0.02, and Fu=0, which are almost identical to the theoretical expectations in the mouse haploid karyotype of Tr(K)=0.9467, In(K)=0.0527, and Fu(K)=0.0006. A close correlation between theoretical and experimental values is also observed in irradiated *Drosophila melanogaster* (Imai et al., 1986). These data strongly suggest that the pattern (relative frequencies) of radiation induced chromosomal mutations is principally the same as that expected by the random-contract-and-exchange model, i.e., centric fusion is extremely rare in a system where rearrangements occur randomly.

The pattern of chromosomal mutations in human cancers is deduced from the data recorded in the monograph by Mitelman (1985). To minimize the bias introduced by the over-reporting of specific common translocations, for example,

t(9;22), t(15;17) and t(8;21), these were eliminated from the estimations. Among 5,345 cases of human cancers, a total of 2,392 structural chromosomal rearrangements were identified, where $Tr=0.9431$, $In=0.0489$ and $Fu=0.0079$ (Table 1). Almost same results were obtained even if we include the specific common translocations, i.e., $Tr=0.9689$, $In=0.0255$ and $Fu=0.0056$. These frequencies are roughly comparable with the experiments by ionizing radiation, except that the relative frequency of centric fusion ($Fu=0.0056$ or 0.0079) is about 28–40 times higher than the theoretically expected value ($Fu(2K)=0.0002$).

c) *Patterns of structural chromosomal mutations
in newborn babies*

The relative frequencies of structural chromosomal mutations in newborn babies were estimated from the chromosomal data of Friedrich and Nielsen (1973), Jacobs *et al.* (1974), Bochkov *et al.* (1974), Nielsen and Sillesen (1975), Hamerton *et al.* (1975) and Maeda *et al.* (1978). Cases were selected in which parental chromosomal studies were performed so that confirmation of *de novo* origin was possible. A total of 92 cases out of 42,023 live born infants were available for the present purpose (Table 2).

It is a surprising finding that the frequency of *de novo* centric fusion in newborns ($Fu(NBdn)=0.2143$) is about 1,000 times higher than the theoretically expected value ($Fu(K)=0.0002$). There is a possibility that the $Fu(NBdn)$ value is biased by gametic and zygotic selection, and if so the $Fu(NBdn)$ value cannot be compared directly with $Fu(K)$. This problem can be minimized theoretically by including only the relative frequencies of balanced forms of the chromosomal mutations that succeeded to fertilize. We use the terms $Tr(f)$, $In(f)$ and $Fu(f)$ for this category. The reasons for this approach are straightforward; balanced rearrangements in man and mouse are virtually uninfluenced by zygotic selection, and the majority of unbalanced forms induced secondarily from balanced forms in meiotic processes are eliminated during the course of embryonic development. This selection is mediated by the imbalance in gene expression resulting from the respective monosomy, trisomy, partial deletion or duplication, etc. (e.g., Chandley, 1981; Dellarco *et al.*, 1985; Gropp *et al.*, 1982; Hassold and Jacobs, 1984). Indeed, balanced aberrations include 90.2% of those found in live born babies (Hook and Hamerton, 1977), and in contrast unbalanced types are found in 88% of rearrangements characteristic of spontaneous abortions (Table 2). Our estimates revealed $Tr(f)=0.8192-0.9004$, $In(f)=0.0992-0.1799$, and $Fu(f)=0.0001-0.0004$, where the ranges are two extremes assuming the minimum and maximum selection pressures (for details see APPENDIX A). Now, we have $Fu(NBdn)/Fu(f)=536-2,143$.

It could be pointed out, however, that the *de novo* mutations detected comprise only 10 translocations and 3 fusions, i.e., less than enough for statistical analyses. To address such a valid criticism, the total (*de novo* plus inherited data) frequency observed in the newborn population (Table 2, column F) could be used. For this

adjustment, let $Fu(NB)$ and $Fu(nb)$, respectively, be the gross frequencies of centric fusion observed in newborn population and that estimated theoretically. From the data considered, $Fu(NB)=0.4457$. $Fu(nb)$ can be estimated by using two parameters, mutation rate (μ) and relative fitness ($1-s$) (Wright, 1941; Crow and Kimura, 1970). This estimation was done by N. T. (for details see APPENDIX B). The result is $Fu(nb)=0.0006$, and thus $Fu(NB)/Fu(nb)=743$. An almost identical result was obtained from the data by Hook and Hamerton (1977; see Table 2, column G), i.e., $Fu(NB)/Fu(nb)=792$. Based on these series of estimations, we conclude that centric fusion appears in human germ cells at least 500–1,000 times higher than the frequency expected by the random-contact-and-exchange model. This phenomenon is designated here as the "fusion burst".

2) *The fusion burst in some populations of European feral mice (Mus musculus domesticus)*

According to the listings by Searle (1981) and the more recent publication by Winking (1986), a total of 162 centric fusions have been found in 23 populations of European feral mice, of which the composition of 76 is unique. No reciprocal translocations or inversions have been reported from these same populations. An unexplained dominance of centric fusion was also found in laboratory mouse stocks, i.e., 12 fusions and 2 translocations (Searle, 1981).

The pattern of chromosomal mutations in radiation experiments is, however, quite different from that found in the feral mice mentioned above. In the list by Searle, 38 cases of reciprocal translocations and 6 cases of inversions are recorded, but there is no report of centric fusion. Their frequencies are, therefore, $Tr=0.86$, $In=0.14$ and $Fu=0$. One of us (Y.M.) reconfirmed this same tendency in X-ray induced chromosome aberrations in murine oocytes and sperm, i.e., $Tr=0.9416$ (in terms of dicentric chromosomes), $In=0.0584$ (ring chromosomes), and $Fu=0$ (Table 3). These patterns of relative frequencies are highly consistent with those expected by the random-contact-and-exchange model ($Tr(K)=0.9467$, $In(K)=0.0527$ and $Fu(K)=0.0006$), which was estimated using 10 metaphases from bone marrow cells of a BALA/c male. Note that dicentric and ring chromosomes are incomplete types of reciprocal translocation and inversion, respectively. If the ratio of frequencies of balanced and unbalanced types is constant between these rearrangements, it is possible to estimate Tr and In based on the relative frequencies of the unbalanced types. For simplifying discussion, we used here a mean frequency of oocytes and sperm. However, the frequency of translocation in oocytes ($Tr=0.87$) is significantly lower than in sperm ($Tr=0.98$). This may be resulting from a difference of chromosomal configuration in each cell, i.e., chromosome configuration is non-random in oocytes due to the hammock structure, but they are packed more compactly in sperm and thus interaction of non-homologous chromosomes predominates.

To determine the pattern of spontaneous chromosomal mutations in mouse germ

Table 3. *The probabilities of occurrence of structural chromosomal mutations in the mouse haploid karyotype (K) and their relative frequencies in European feral mice, radiation induced chromosomal mutant stocks, and X-ray induced chromosomal aberrations in oocytes or sperm*

Type of chromosomal mutations	A	B	C	D		
	Theoretical expectation (K)	European feral mice* (<i>M. m. domesticus</i>)	Radiation induced chromosomal mutant stocks*	X-ray induced chromosomal aberrations in		
				oocytes	sperm	Total**
Reciprocal translocation (Tr)	Tr (K)					
	0.9467	0.0 (0)	0.86 (38)	0.87 (75)	0.98 (167)	0.9416 (242)
Inversion (In)	In (K)					
	0.0527	0.0 (0)	0.14 (6)	0.13 (11)	0.02 (4)	0.0584 (15)
Centric fusion (Fu)	Fu (K)					
	0.0006	1.0 (76)	0.00 (0)	0.00 (0)	0.00 (0)	0.0000 (0)

* Searle (1981)

** This experiment was done by Y. M.

cells, we surveyed chromosomes from adult male testes. A total of 3,000 male mice were utilized in this work involving 32 inbred strains (1,997 males), 8 *Mus musculus subspecies* (828), and their hybrids (175) (Table 4). Chromosomal abnormalities were detected in 7 mice (Tables 5 and 6). Four of them were mosaic, two for Y disomy (No. 148 and 441), and one each for minute Y (No. 1,238) and autosomal trisomy (No. 2,797). The remained three had constitutional mutantions; two were reciprocal translocation heterozygotes (No. 834 and 2,985) and one had a trisomy of chromosome No. 10 (Mouse 636) (Table 6). So far as our chromosomal survey is concerned, no centric fusion was observed. Although we need to accumulate more data, our result does not seem to be inconsistent with the theoretical expectation for chromosomal aberration patterns induced by radiation.

How is the fusion burst in European feral mice (more than 1,500 times higher than the theoretical expectation in Table 3) to be evaluated? Such an extraordinary phenomenon cannot be interpreted simply by the stability of fusion to selection. Gropp *et al.* (1982) showed that fertility was reduced by 4–28% in males and 6–34% in females (in terms of the frequency of unbalanced types induced by non-disjunction) for heterozygotes bearing a single fusion, and that conversely it became 60–80% or nearly 100% of normal in heterozygotes bearing multiple fusions with monobrachial homology accompanying chain formation at pachytene. Of course, there is a possibility that if effective population size is significantly small, most centric fusions will be fixed by random drift (Wright,

Table 4. *Materials used for the survey of spontaneous chromosomal mutations in mice**

1. INBRED STRAINS			2. FERAL MICE (<i>Mus musculus</i>)		
AJ	12	ICR	20	<i>M. m. bactrianus</i>	20
AKR	19	KK	1	<i>M. m. brevirostris</i>	36
A/Wy	144	LP/J	15	<i>M. m. castaneus</i>	132
AU	5	LT/Sv	19	<i>M. m. Chinese subspecies</i>	54
BALB/cAnN	73	MA	3	<i>M. m. domesticus</i>	260
BDP/J	7	NC	8	<i>M. m. molossinus</i>	248
B6	2	NZB/BINJ	7	<i>M. m. musculus</i>	65
CBA	68	PL/J	13	<i>M. m. urbanus</i>	13
C57BL/10Sn	1054	RfM	3	subtotal	828
C57BL/6J	33	SJL/J	26		
C57BR/cdJ	22	SK/Cam	22	3. INTER-SUBSPECIES HYBRIDS	
C58/J	2	SM/J	5	B10 x <i>M. m. molossinus</i>	70
C3H/He	208	SWR/J	8	B10 x <i>M. m. Chinese subspecies</i>	26
DBA/1J	43	WB/Re	46	BALB/c x <i>M. m. molossinus</i>	79
DBA/2J	38	129	29	subtotal	175
DDK	3				
HTG	39	subtotal	1997	TOTAL (1+2+3)	3000

* This experiment was done by H. T. I. and K. M.

Table 5. *Male mice with chromosomal abnormalities*

Individual mouse	Strain	Cytological remarks	Fertility
148	<i>M. m. castaneus</i> (M. CAS. QZN)	40XY/41XYY Y disomy (mosaic)	—
441	<i>M. m. castaneus</i> (M. CAS. QZN)	40XY/41XYY Y disomy (mosaic)	+ (normal)
636	C3H/He	41XY No. 10 trisomy	—
834	C57BR/cdJ	Reciprocal translocation	—
1238	C57BL/10Sn	40XY/40XY ^m minute Y (mosaic)	—
2797	<i>M. m. musculus</i> (M. MUS. NJL)	40XY/41XY Autosomal trisomy (mosaic)	—
2985	C57BL/10Sn	Reciprocal translocation	+

For materials used see Table 4.

Chromosomal abnormalities were detected by examining the chromosome number, shape, and configurations in 5–10 cells at each stage of spermatogonia, MI and MII. If there were some abnormalities, we reconfirmed by more detailed chromosomal observations, and each aberrant male was mated with 3 virgin female mice of the same strain or subspecies for testing fertility. Those mice having extremely small sized testes (26–0 mg) were examined by using bone marrow cells.

Table 6. *Cytological data of the male mice with*

Ind. No.	Spermatogonia (2n)				Diakinesis-	
	39	40	41	42	19 (XY)	20 (XY)
148	0	9	15	0	0	1
441	0	19	7	0	0	50
	(bone marrow)					
636	0	1	33	3	—	—
834	0	12	0	0	50	0
1238	9 (Y ⁻)	24 (Y ₁ ^m)	3 (2Y ₁ ^m)	0	0	20 (XY ⁻)
	14 (Y ₂ ^m)					
	(lung culture)					
	45 (Y ⁻)	13 (Y ₂ ^m)	1 (Y ₁ ^m , Y ₂ ^m)	0	—	—
		1 (Y ₁ ^m)	2 (2Y ₁ ^m)	0		
		1 (Y)				
	(bone marrow)					
2797	9 (XY ⁻)	30 (XY)	5 (XYY)	0	—	—
2985	0	20	0	0	50	5

1941; Crow and Kimura, 1970; Bengtsson and Bodmer, 1976a). This argument is, however, rather sophisticated in the present case, since, if chromosomal mutations occur at random, about 95% of structural aberrations are reciprocal translocations, about 5% for inversion and centric fusion accounts for only 0.06% (Table 3). As fixation rate is equal to occurrence rate in a small sized population, at least inversions should be fixed more frequently than fusions (for details see APPENDIX B). The alternative is to assume the non-random appearance of centric fusion in mice as well as the case of human newborn babies, which is discussed in the next section.

3) *A possible mechanism for the fusion burst*

a) *The concept of telomere fusion*

Centric fusion has long been considered as a special case of reciprocal translocation, with the breakpoint occurring in the pericentromeric heterochromatin of acrocentrics, and with the accompanying loss of a centric heterochromatic minute (White, 1954, 1973; John and Freeman, 1975). There is, however, accumulating evidence that most centric fusions in man fall into the category of "telomere fusion" (Fig. 1). The metacentric chromosomes induced by this type of rearrangement are dicentric (Fig. 1), but they are stable by the suppression of one centromere (Niebuhr, 1972; Warburton *et al.*, 1973; Daniel and Lam-Po-Tang, 1976; Daniel, 1979). This scenario also probably occurs in the mouse, since no loss of constitutive heterochromatin is detected in metacentrics induced by centric fusion (Redi *et al.*, 1986).

Mechanisms for centric fusion in man have been proposed by Kurnit (1979), Stahl *et al.* (1983), and Guichaoua *et al.* (1986). These models, despite outward

chromosomal abnormalities summarized in Table 5

Metaphase I (n)				Metaphase II		
20 (X/Y)	21 (X/Y)	21 (XY//Y)	20 (X or Y)	21 (YY)	21 (XY)	22 (X, Y, Y)
0	0	13	0	1	1	0
0	10	22	28	6	0	1
—	—	—	—	—	—	—
15	0	0	16	0	0	0
0	89 (X/Y ₁ ^m)	0	0	0	0	0
—	—	—	—	—	—	—
—	—	—	—	—	—	—
8	0	0	36	0	0	0

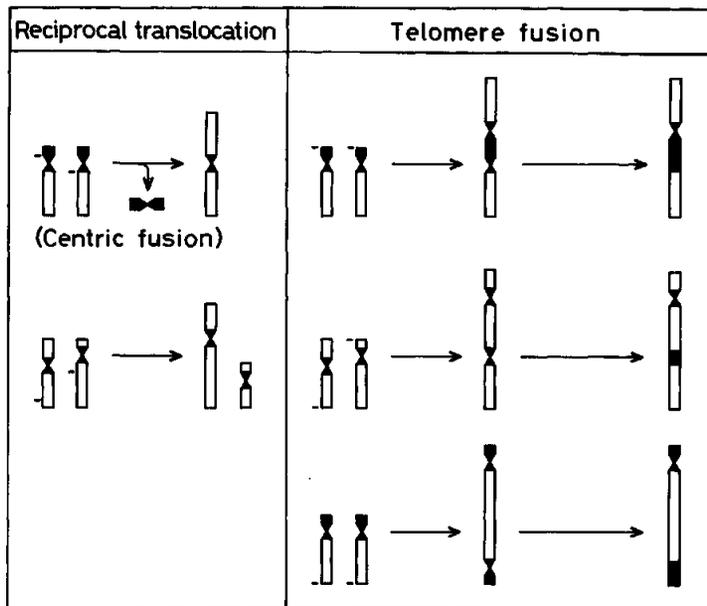


Fig. 1. Schematic representation of ordinal reciprocal translocations including centric fusion, and a new category of rearrangement "telomere fusion" accompanying centromeric inactivation. Small bars indicate exchange sites. Black parts mean constitutive heterochromatin. Active centromeres are represented by primary constriction. For the mechanism of telomere fusion see Fig. 2.

dissimilarity, all assume the following two processes, (1) the physical proximity of telomeres of two non-homologous acrocentrics, and (2) a DNA exchange between

telomeres (or more precisely telomere regions).

In the present study a more generalized model for centric fusion is proposed, based on the hammock structure. It is well recognized that, at interphase, chromosome of eukaryotes are anchored on the nuclear membrane by telomeres, (for documentation in man see Holm and Rasmussen, 1977, and for other species see Rasmussen and Holm, 1980, and von Wettstein *et al.*, 1984). This non-random chromosomal configuration was first termed the suspension arch structure (Imai *et al.*, 1986), and later the hammock structure (Imai *et al.*, 1988). Under the hammock structure, if telomeres are fixed on the nuclear membrane at a distance great enough, they will not be able to interact (exchange DNA) with each other. This is probably the reality of cellular topography, that corresponds to the unipolarity of telomeres proposed long ago by Muller (1938).

b) *Modes of telomere fusion*

When heterochromatic and euchromatic arms are denoted H and E, three types of arm associations are theoretically possible by telomeric fusion (E-E, E-H and H-H associations) (Fig. 2). If DNA exchange occurs at the telomere-nuclear membrane junction (Fig. 2), the cytological expectation is such a fusion.

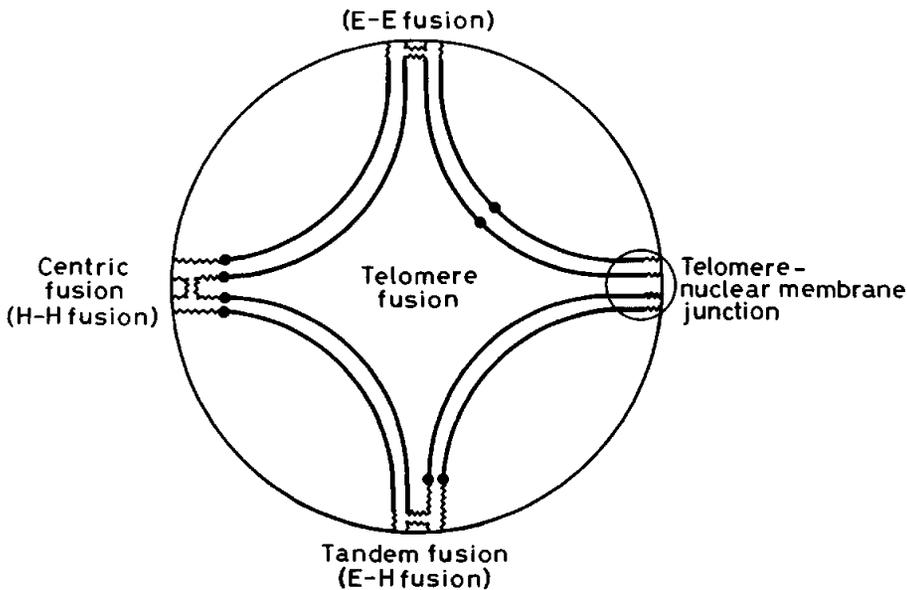


Fig. 2. A possible mechanism of telomere fusion based on the hammock structure. When the telomeres of euchromatic and heterochromatic arms are denoted E and H, respectively, three types of telomere fusions (E-E, H-H and E-H fusion) are theoretically possible. We assume a physical proximity of telomeres on the nuclear membrane and DNA strand exchanges by a miss of telomere replication. Notched lines represent constitutive heterochromatin in short arms or telomeres. Solid circles are centromere. H-H fusion and E-H fusion are synonymous with centric fusion and tandem fusion, respectively. The frequencies of the three types actually observed are H-H fusion > E-H fusion > E-E fusion, indicating that euchromatic terminals are more stable than heterochromatic ones.

Robertsonian translocation (or Robertsonian fusion) is H-H fusion in this terminology, and E-H fusion corresponds to tandem fusion or tandem translocation. E-E fusion is synonymous with terminal rearrangement (TA) by Borgaonkar (1984). According to the catalog of chromosomal variants by Borgaonkar, Robertsonian translocation (TR; in the present term H-H fusion), tandem translocation (TX; E-H fusion), and terminal rearrangement (TA; E-E fusion) are reported in 124 cases, 26 cases, and 8 cases in man, respectively. In these data there is gross under-reporting of "regular" TR such as tdic(13; 14) or tdic(14; 21); even so these data suggest that euchromatic terminals tend to be more resistant to telomere fusion than heterochromatic terminals are.

The tendency for more H-H fusions is also found in mouse, e.g., the 76 independent fusion found by Gropp et al. (1972) and Capanna et al. (1976) are H-H fusions in the present classification. On the other hand, H-H fusion, H-E fusion, E-E fusion observed in mouse L cells are in the ratio of 13:6:0 (according to the figures by Lau and Hsu, 1977, and Rattner and Lin, 1985). Further details of centric fusion are discussed in the next section which concerns karyotype evolution.

4) *A possible biological significance of the fusion burst in karyotype evolution*

According to the minimum interaction hypothesis, centric fusion would occur frequently in acrocentric karyotypes to reduce the number of "unstable telomeres". This idea was first proposed by Imai et al. (1988) in ant karyotype evolution. The outline is as follows.

a) *Telomere instability in telocentric chromosomes*

Telocentric chromosomes induced by centric fission in classical cytogenetics are thought to be unstable, because the naked chromosome ends produced by fission would lack stable telomeres. This is one of the reasons why fission has been unacceptable to some cytologists for many years. As the *de novo* appearance of telomeres is inevitable in any fission hypothesis, Imai et al. (1977) proposed the concept of "dormant telomeres", based on the palindrome model of the telomere (Cavalier-Smith, 1974; Bateman, 1975) and the uniform distribution of palindromes on chromosomes (e.g., Thomas et al., 1973; Wilson and Thomas, 1974). In this concept, potentially naked chromosomal ends would not be produced by fission if dormant telomeres (=certain interstitial palindromes) were present. In spite of the recent advances in analyses at the molecular level of centromeric and telomeric structures in lower eukaryotes (see Blackburn and Szostak, 1984 for a review), those of higher organisms are still virtually unknown (Richards and Ausubel, 1988; Allshire et al., 1988).

If telomeric structures are essential for stable chromosome ends, possible mechanisms may be either *de novo* formation of telomeres in the literal sense or the reorganization of proximally located DNA (i.e., the centromere itself and pericentromeric heterochromatin) to form such structures. The latter may be

attractive, because elongation of heterochromatic short arms by tandem growth of constitutive heterochromatin (t.g.c.h.) has actually occurred in acrocentric chromosomes of ants (Imai *et al.*, 1977; 1988). There is cytological evidence suggesting a substantial difference between the terminals of euchromatic arms and those of heterochromatic ones, i.e., in mouse spermatogenesis euchromatic terminals associate end-to-end stably until the end of the first meiotic metaphase (MI), whereas heterochromatic terminals often dissociate before MI (Imai and Moriwaiki, 1982). It is a noteworthy characteristic that these constitutively heterochromatic arms associate nonspecifically in interphase nuclei, which induces a non-random distribution of acrocentric chromosomes (Fig. 3c). The Monte Carlo simulation experiments revealed that the genetic risk by reciprocal translocation increases in such acrocentric karyotypes in spite of their high chromosome numbers (for details see APPENDIX C). Note that centric fusion is a kind of translocation. This means in other words that, although we could not discrimin-

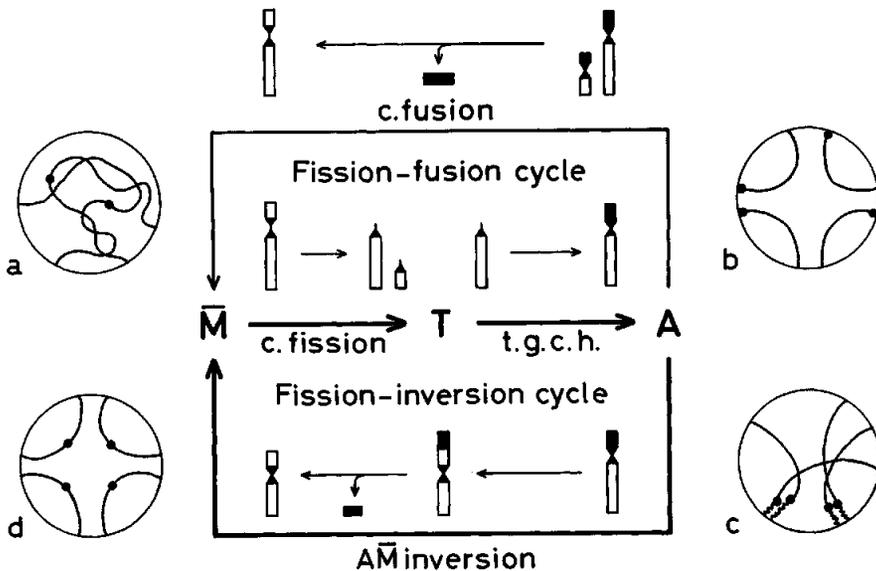


Fig. 3. Fission-inversion cycle and fission-fusion cycle in chromosome evolution with illustrations of chromosome configuration in low-numbered metacentric (a), high-numbered telocentric (b), high-numbered acrocentric (c), and high-numbered metacentric (d) karyotypes. The karyotype d is stable, but a and c are unstable from the viewpoint of the minimum interaction hypothesis (Imai *et al.*, 1986). The fission-inversion cycle is evolutionarily more advantageous than the fission-fusion cycle, because karyotypes alter $a \rightarrow b \rightarrow c \rightarrow d$ in the former, whereas $a \rightarrow b \rightarrow c \rightarrow a$ in the latter. \bar{M} ; metacentrics in a broad sense including conventional M, SM or ST. T; telocentric. A; acrocentric. For the definition of \bar{M} , T and A see Imai (1975 and 1976). $A\bar{M}$ inversion; inversion changing from an acrocentric to a metacentric. the reverse inversion ($\bar{M}A$ inversion) occurs in a stochastic sense negligibly rarely (Imai and Maruyama, 1978), and such unidirectionality of inversion was supported by the cytological evidence that most of all acrocentrics have totally heterochromatic short arms (also see Imai, 1986). t.g.c.h.; tandem growth of constitutive heterochromatin.

ate centric fusion from other translocations in the present simulation, the probability of occurrence of centric fusion might increase by such a physical proximity of acrocentrics.

b) *Risk-avoidance mechanisms for telomere instability*

There are at least two possible mechanisms for minimizing the genetic risk resulting from the physical proximity of chromosomes during meiosis. One of these is by chromosomal alteration as in $A\bar{M}$ inversion (p.i.($A\bar{M}$)) and the other is by centric fusion (Fig. 3). The former can change an acrocentric karyotype (Fig. 3c) into a metacentric one (Fig. 3d). As constitutive heterochromatin is eliminated by $A\bar{M}$ inversion, and if an interstitial palindromic telomere is proximally available, a stable metacentric chromosome can be expected. In the metacentric karyotype shown in Fig. 3d, the probability of occurrence of reciprocal translocation will be markedly reduced because of the minimized interaction of chromosomes. These series of chromosomal changes are termed the "fission-inversion cycle".

On the other hand, if the acrocentrics take part in centric fusion (H-H fusion in the present text), the result is also a metacentric karyotype. In this case, constitutive heterochromatin is eliminated as in the case of $A\bar{M}$ inversion, and thus the unstable telomeres will be removed. However, in the fusion induced metacentric karyotype, the size of chromosomes increases again. Now, we are right back where we started (Fig. 3a), and this alternative cycle termed the "fission-fusion cycle". The fusionists will say, this is the scenario actually occurring in man and mouse, which is termed here as the fusion burst. The fissionists will, however, predict that metacentrics induced by centric fusion will change again into telocentrics by centric fission, and that a fission-fusion fluctuation will continue until all chromosomes become stable metacentrics by $A\bar{M}$ inversion (Fig. 3d). The fission-fusion cycle (or the fusion burst) is by this means a transient step in long-term karyotype evolution by the fission-inversion cycle as suggested in ants (Imai et al., 1988).

c) *A heterodox but nonnegligible possibility for
the fusion burst in man and mouse*

The fusion burst may be easy to assume in ants because of finding pseudo-acrocentrics (A^M). Pseudo-acrocentrics are defined as acrocentrics having extraordinarily elongated heterochromatic short arms due to tandem growth of constitutive heterochromatin (t.g.c.h.). Indeed, such heterochromatic short arms are often longer than euchromatic long arms in *Myrmecia pilosula* (Imai et al., 1988). Therefore, in karyotypes with A^M s, chromosomal interactions will accelerate remarkably by non-specific associations of heterochromatic short arms.

The size of acrocentric short arms is, however, usually small in man and mouse (i.e., less than 0.6% against genome size). Besides, there is another negative evidence that centric fusion has seldom been observed in radiation experiments in man and mouse (Tables 1, and 3). These data suggest that physical proximity of

chromosomes, due to the non-specific association among heterochromatic short arms, would not contribute itself to such a high incidence of centric fusion found in human newborn babies and European feral mice. Other factors must be involved.

In this connection, it is an interesting phenomenon that telomeric fusions appear frequently in some neoplastic processes, such as long-term cultured mouse L cells (Hilwig and Gropp, 1973; Lau and Hsu, 1977; Rattner and Lin, 1985) or mouse myeloma cell lines (Shepard *et al.*, 1974). A high incidence of centric fusion is also present in canine venereal tumors (Sasaki *et al.*, 1974). In human cancers, centric fusion is about 28–40 times the theoretically expected value (Mitelman, 1985; Table 1). E-E, E-H, and H-H fusions have been frequently observed in culture plant cells of celery (Murata and Orton, 1984), whereas no fusions are found in their root tip cells (Murata, personal communication). In the case of European feral mice, centric fusions have appeared characteristically in the hybridization zone between *Mus musculus domesticus* and *M. m. musculus* (Winking 1986) and some authors assume a mutagenic agent or a certain heritable factor or an infectious factor (e.g., Sage, 1981; Moriwaki *et al.*, 1984). Our survey of chromosomal abnormalities in the mouse (Table 5) is consistent with these data, i.e., centric fusion is a rare event in normal inbred mouse strains, and even in feral mice other than the European feral mice at the hybridization zone between *M. m. musculus* and *M. m. domesticus*, or their secondarily derivatives by introgression.

These examples suggest that, in spite of a frequent NOR (satellite) association (Nakagome, 1969; van Hemel, 1971), Rab1 configuration (Cremer *et al.*, 1982), telomere-telomere attachment (Sved, 1966; Ashley and Pocock, 1981), or the so-called bouquet configuration, telomeres are usually protected safely from chromosomal rearrangements. However, telomeric fusions occur often under some specific conditions such as long-term cell culture, tumorigenesis, or infection by virus/transposon like or unknown factors other than ionizing radiation. These factors, if there were, would preferentially attack the telomere-nuclear membrane junction (Fig. 2), and would disrupt the telomere replication system. It is not known which of these factors (if any) contributes to the high frequency of fusions in human newborns, but we need to call attention to such a possibility. This suggests that caution is necessary before invoking the fusion burst in man and mouse as the “strong” supporting evidence for the predominance of centric fusion in mammalian karyotype evolution.

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APPENDIX A

Estimation of the relative frequency of balanced type chromosomal mutation at fertilization

We assume a postmating selection; i.e., unbalanced type chromosomal mutations are eliminated during embryonic stages, while mutations with balanced types can grow up to adults without selection (for details see text). In this assumption, the relative frequency of balanced types at fertilization is essentially important for evaluating the frequency of chromosomal mutation in adults.

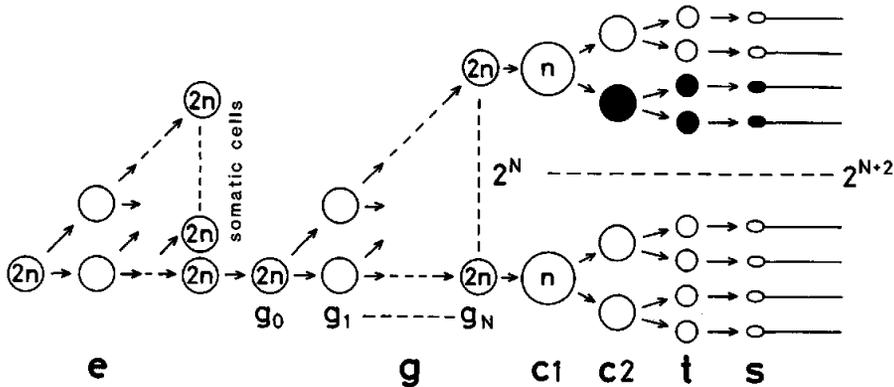


Fig. 4. Schematic representation of spermatogenesis for estimating effective rates of balanced type chromosomal mutations at fertilization. e; early embryonic cell. $g_0 \dots g_N$; spermatogonia. c1; 1st spermatocyte. c2; 2nd spermatocyte. t; spermatid. s; sperm. n and 2n; haploid and diploid chromosome number. We also use K and 2K in the text for haploid and diploid karyotypes based on the definition by Imai and Crozier (1980). Solid circles represent cells with a balanced type chromosomal mutation.

We consider only spermatogenesis (Fig. 4), but the same argument is applicable to oogenesis. Each cell generation of spermatogonia is represented as g_0 (primordial germ cell), g_1, \dots, g_N , the total number of cells at g_N begins 2^N . Note that at g_N , there are 2^{N-i} descendants of a cell which occurred at the i -th generation (g_i). The frequency of cells at g_N descended from a mutant which occurred at the i -th generation (denoted here P_i) is, therefore,

$$P_i = 2^{N-i} / 2^N = 1/2^i = 1/n_i \tag{A1}$$

where $n_i \equiv 2^i$.

Let $Q_{gN}(A_j)$ be the frequency of mutant type A_j ($A_{j=1}$; reciprocal translocation, $A_{j=2}$; inversion, $A_{j=3}$; centric fusion) in spermatogonia as g_N when such mutation occurs at the i -th cell generation. We also define $R_{gi}(A_j)$ as per-cell-generation rate of mutant type A_j in spermatogonia at the i -th cell generation (we discuss the case of $i=0$ later). We assume that *de novo* chromosomal mutations are always complete type (i.e., balanced type). By these definitions and assumptions, we have

$$Q_{gN}(A_j) = R_{gi}(A_j) n_i \cdot P_i = R_{gi}(A_j) \tag{A2}$$

Namely, the frequency is equal to the rate of occurrence of chromosomal mutations. The frequency of balanced type A_j which occurs at spermatogonia and is transmitted to sperm, denoted $Q_{g \rightarrow s}(A_j)$, is

$$Q_{g \rightarrow s}(A_j) = \beta(A_j) \cdot Q_{gN}(A_j) = \beta(A_j) \cdot R_{gi}(A_j) \tag{A3}$$

where $\beta(A_j) = \beta_{c1}(A_j) \cdot \beta_{c2}(A_j)$, and represents the fraction of gametes with balanced

A_j type mutation, which is adjusted by estimating unbalanced A_j types induced secondarily from balanced types during the 1st (c1) and 2nd (c2) meiotic divisions (see the diagrams showed in Figs 5–8). The results are $\beta(A_{j=1})=1/4$, $\beta(A_{j=2})=1/2$, and $\beta(A_{j=3})=1/2$ to $1/6$. In $\beta(A_{j=3})$, $1/2$ and $1/6$ are the two extreme cases for normal disjunction and non-disjunction. We assume that eggs are always normal at fertilization. The frequency of balanced A_j type which occurs at spermatogonia and succeeds to fertilize [termed $Q_{g \rightarrow f}(A_j)$] is then given

$$Q_{g \rightarrow f}(A_j) = Q_{g \rightarrow s}(A_j) = \beta(A_j) \cdot R_{gi}(A_j) \quad A4$$

In text, we have used different symbols, $Tr(g)$, $In(g)$ and $Fu(g)$ instead of $R_{gi}(A_{j=1,2,3})$, and $Tr(g \rightarrow f)$, $In(g \rightarrow f)$ and $Fu(g \rightarrow f)$ instead of $Q_{g \rightarrow f}(A_{j=1,2,3})$. Thus we have $Tr(g \rightarrow f) = Tr(g)/4$, $In(g \rightarrow f) = In(g)/2$ and $Fu(g \rightarrow f) = Fu(g)/2$ to $Fu(g)/6$.

The same results are obtained for early embryonic cells (termed e in Fig. 4). Let $Q_{e \rightarrow f}(A_j)$ be the relative frequency of balanced type A_j mutation which occurs at early embryonic cells (e) and succeeds to fertilize. $Q_{e \rightarrow f}(A_j)$ is given by

$$Q_{e \rightarrow f}(A_j) = \beta(A_j) \cdot R_{g0}(A_j). \quad A5$$

The difference between A3 and A5 is that $R_{g0}(A_j)$ is defined as the gross mutation rate from fertilization to a primordial germ cell, while $R_{gi}(A_j)$ ($i \geq 1$) as the mutation rate per-cell-generation.

The relative frequency of balanced type A_j which occurs at 1st spermatocyte (c1), 2nd spermatocyte (c2), spermatid (t) and sperm (s), and succeeds to fertilize is respectively given by

$$Q_{c1 \rightarrow f}(A_j) = \beta(A_j) R_{c1}(A_j) \cdot 2^N \cdot (1/2^N) = \beta(A_j) R_{c1}(A_j) \quad A6$$

$$Q_{c2 \rightarrow f}(A_j) = \beta_{c2}(A_j) R_{c2}(A_j) \cdot 2^{N+1} \cdot (1/2^{N+1}) = \beta_{c2}(A_j) R_{c2}(A_j) \quad A7$$

$$Q_{t \rightarrow f}(A_j) = R_t(A_j) \cdot 2^{N+2} \cdot (1/2^{N+2}) = R_t(A_j) \quad A8$$

$$Q_{s \rightarrow f}(A_j) = R_s(A_j) \cdot 2^{N+2} \cdot (1/2^{N+2}) = R_s(A_j) \quad A9$$

The results indicates that relative frequency of chromosomal mutations is principally the rate of occurrence of such mutations, though it should be adjusted by the rate of non-disjunction at the 1st and 2nd meiotic divisions which induce unbalanced types from balanced types [$\beta(A_j)$]. It is noteworthy that $\beta(A_j)$ is variable by chromosomal mutations. If we assume chromatid type exchanges, then $\beta(A_{j=1})=1/16$, $\beta(A_{j=2})=1/4$ and $\beta(A_{j=3})=1/4$ to $1/36$ (Figs 5–8). On the other hand, if chromosome type exchanges occur at the 1st spermatocyte (termed c1'), we can expect $\beta(A_{j=1})=1/4$, $\mu(A_{j=2})=1/2$ and $\beta(A_{j=3})=1/2$ to $1/6$ as in the case of spermatogonia mentioned above.

Finally, based on $Q_{x \rightarrow f}(A_j)$ we estimate the relative frequency of balanced type mutations at fertilization [symbolized as $Q_{x \rightarrow f}(A_j)'$], where x stands for e, g, c1, c2, t and s. $Q_{x \rightarrow f}(A_j)'$ is estimated as follows;

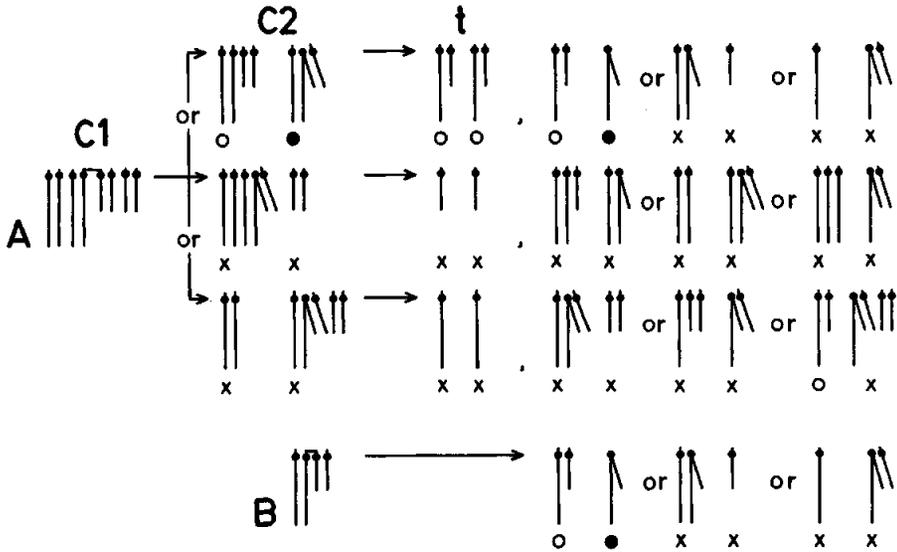


Fig. 5. Schemes for estimating $Q_{c1 \rightarrow f}(Fu)$ (A) and $Q_{c2 \rightarrow f}(Fu)$ (B) (the effective rate of balanced type centric fusion which occurs in c1 or c2 and succeeds to fertilize). \circ ; homozygous for normal chromosomes. \bullet ; heterozygous for a chromosomal mutation (balanced type). x; unbalanced type accompanying nullisomy (monosomy after fertilization) or disomy (trisomy). Solid circles on chromosomes represent centromeres. We assume in this figure a chromatid type exchange. For the chromosome type exchanges see Fig. 6. For details see APPENDIX A and Table 7.

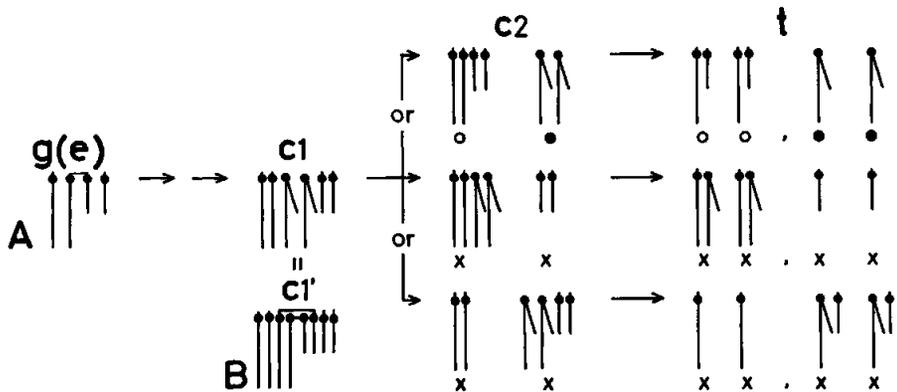


Fig. 6. Schemes for estimating $Q_{e \rightarrow f}(Fu)$ and $Q_{g \rightarrow f}(Fu)$ (A) or $Q_{c1' \rightarrow f}(Fu)$ (B). We use c1' if chromosome type mutations occur in the 1st spermatocyte. The karyotype symbolized by c1' is exactly the same with that of c1 bearing metacentrics which were induced at spermatogonia (g) or early embryonic cells (e). For details see APPENDIX A, Table 7, and Fig. 5.

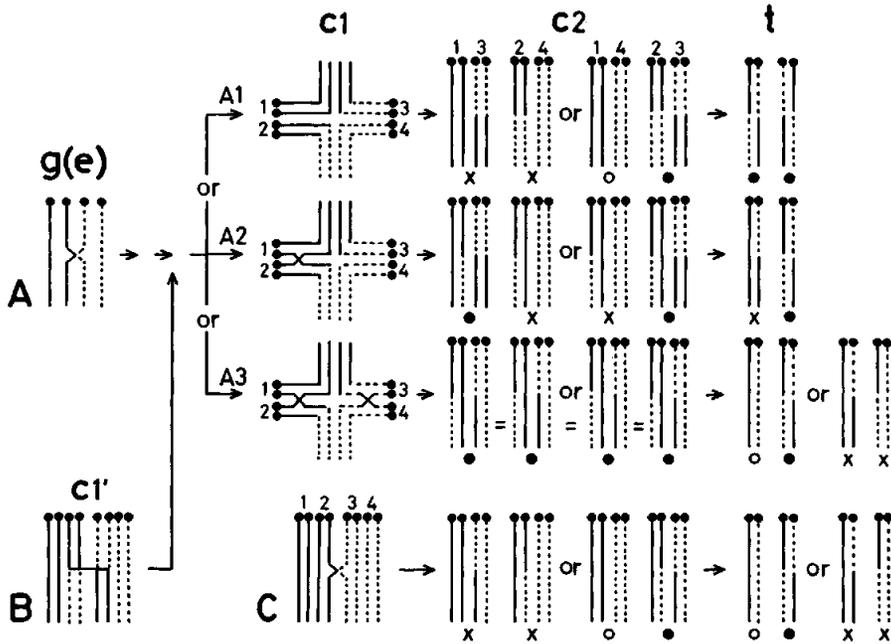


Fig. 7. Schemes for estimating $Q_{e \rightarrow f}(Tr)$ and $Q_{g \rightarrow f}(Tr)$ (A) or $Q_{c1' \rightarrow f}(Tr)$ (B) or $Q_{c1 \rightarrow f}(Tr)$ (C). Chromosome configurations at $c1$ are classified into three types by the number of crossing-over, i.e., zero in A1, one in A2 and two in A3. For details see APPENDIX A, Table 7, and Fig. 5.

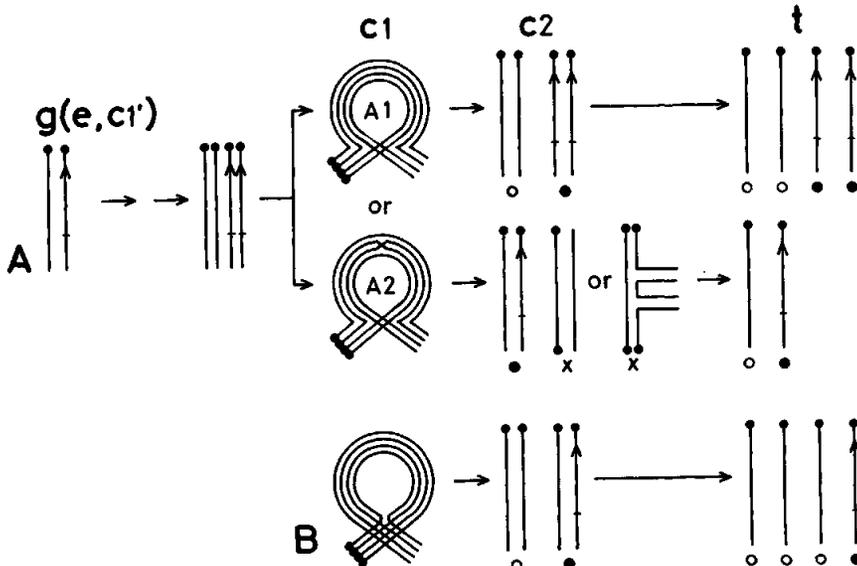


Fig. 8. Schemes for estimating $Q_{e \rightarrow f}(In)$, $Q_{g \rightarrow f}(In)$ and $Q_{c1' \rightarrow f}(In)$ (A) or $Q_{c1 \rightarrow f}(In)$ (B). In A2, unbalanced types form a chromosome bridge at anaphase II, and thus they cannot mature to sperms. This means in other words that we cannot expect theoretically any unbalanced types in inversion. For details see APPENDIX A, Table 7, and Fig. 5.

$$Q_{x \rightarrow f}(A_j)' = \frac{Q_{x \rightarrow f}(A_j)}{\sum_{j=1}^3 Q_{x \rightarrow f}(A_j)} = \frac{\beta(A_j)R_x(A_j)}{\sum_{j=1}^3 \beta(A_j)R_x(A_j)} \quad A10$$

In the text, we have used Tr, In and Fu for $A_{j=1}$, $A_{j=2}$ and $A_{j=3}$, and also Tr(x), In(x) and Fu(x) instead of $R_x(A_{j=1,2,3})$, and $Tr(x \rightarrow f)$, $In(x \rightarrow f)$ and $Fu(x \rightarrow f)$ or simply Tr(f), In(f) and Fu(f) instead of $Q_{x \rightarrow f}(A_{j=1,2,3})'$. These results are summarized in Table 7.

We estimate $R_x(A_j)'$ for two extreme cases, i.e., $x=c1$ and $c1'$. In table 7, $Q_{c1 \rightarrow f}(Tr) = Tr(c1)/16$, $Q_{c1 \rightarrow f}(In) = In(c1)/4$ and $Q_{c1 \rightarrow f}(Fu) = Fu(c1)/36$, and for $c1'$ $Q_{c1' \rightarrow f}(Tr) = Tr(c1')/4$, $Q_{c1' \rightarrow f}(In) = In(c1')/2$ and $Q_{c1' \rightarrow f}(Fu) = Fu(c1')/2$. From table 2 and formulas 1, 2, and 3 in this text, $Tr(c1) = Tr(c1') = Tr(K) = 0.9477$, $In(c1) = In(c1') = In(K) = 0.0521$, and $Fu(c1) = Fu(c1') = Fu(K) = 0.0002$. Now, we have $Tr(f) = 0.8192 \sim 0.9004$, $In(f) = 0.0992 \sim 0.1799$, and $Fu(f) = 0.0001 \sim 0.0004$.

APPENDIX B

Estimation of the relative frequencies of structural chromosomal mutations in the human newborn and wild mouse populations

Consider a particular type of structural chromosomal mutations, and assume the frequency in a population to be q . The homozygotes with respect to normal and mutant chromosomes produce gametes with only their own types. On the other hand, the heterozygote that carries normal and mutant chromosomes (so-called balanced type) produces three different types of gametes, their frequencies being x_1 for normal type, x_2 for balanced type, and x_3 for unbalanced type ($x_1 + x_2 + x_3 = 1$). In the gamete pool, there are a normal type with frequency $g_1 = p^2 + 2pqx_1$, a balanced type with frequency $g_2 = 2pqx_2 + q_2$, and an unbalanced type with frequency $g_3 = 2pqx_3$ (where $p = 1 - q$). The relative fitness of individuals is assumed to be 1 for those developed from the zygotes that do not carry an unbalanced type, and 0 for those from the zygotes that do carry at least one unbalanced type.

The frequency of balanced type in the next generation becomes

$$q' = \frac{g_2}{g_1 + g_2} \quad B1$$

If we assume that $x_1 = x_2$ and $x_3 = s$ is much smaller than 1, we have the per-generation difference in q , denoted by Δq , to be

$$\Delta q = -spq(1 - 2q) \quad B2$$

as usually used (e.g., Lande, 1979).

Using B1, we first consider the case where a balanced type is polymorphic due to mutation-selection balanced in a large population. Then B2 may be replaced

Table 7. *Effective rates of balanced structural (chromosomal) mutations at fertilization which occurs at a certain cell stage (x) and succeeds to fertilize $Q_{x \rightarrow f}$ ($A_{j=1,2,3}$)*

Type of chromosomal mutations	Cell stages in which chromosomal mutations occur						
	Early embryonic cell (e)	Spermatogonia (g)	Spermatocyte I (cl')	Spermatocyte I (cl)	Spermatocyte II (c2)	Spermatid (t)	Sperm (s)
Reciprocal translocation $Q_{x \rightarrow f}$ (Tr)	Tr (e) /4	Tr (g) /4	Tr (cl') /4	Tr (cl) /16	Tr (c2) /4	Tr (t)	Tr (s)
Inversion $Q_{x \rightarrow f}$ (In)	In (e) /2	In (g) /2	In (cl') /2	In (cl) /4	In (c2) /2	In (t)	In (s)
Centric fusion $Q_{x \rightarrow f}$ (Fu)	Fu (e) /2 Fu (e) /6	Fu (g) /2 Fu (g) /6	Fu (cl') /2 Fu (cl') /6	Fu (cl) /4 Fu (cl) /36	Fu (c2) /2 Fu (c2) /6	Fu (t)	Fu (s)

Tr (x), In (x), and Fu (x); the probability of occurrence of reciprocal translocation, inversion and centric fusion in the cell stage x, respectively. For details see APPENDIX A and Figs 5, 6, and 7.

x stands for e, g, cl', cl, c2, t, and s.

$A_{j=1} = \text{Tr}$, $A_{j=2} = \text{In}$, and $A_{j=3} = \text{Fu}$.

cl' is used for chromosome type mutations, and cl for chromatid type exchanges, occurring at pachytene.

$$\Delta q = -spq(1-2q) + \mu p \quad \text{B3}$$

where a mutation is assumed to occur unidirectionally from a normal type to a balanced type with the per-generation rate being μ . At equilibrium ($\Delta q=0$), we obtain

$$\bar{q} = 1, \frac{1}{4}(1 \pm \sqrt{1-8\mu/s}). \quad \text{B4}$$

There are two stable equilibrium when $8\mu/s < 1$, but since we assume that initially $q=0$, our interest is the equilibrium frequency

$$\bar{q} = \frac{1}{4}(1 - \sqrt{1-8\mu/s}) \quad \text{B5}$$

$$\cong \mu/s \quad \text{for } \mu/s \ll 1.$$

There are three different types of structural chromosomal mutations. To specify them, we use a subscript i ($i=1$ for reciprocal translocation, $i=2$ for inversion, and $i=3$ for centric fusion). Letting \hat{Q}_i be the relative frequency of the i -th type among the rearrangements, we have

$$\hat{Q}_i = \frac{\mu_i'/s_i}{\sum_{i=1}^3 \mu_i'/s_i} \quad \text{B6}$$

from B5, where $\mu_i' = \mu_i/C$ (C is constant). In human newborn babies, $\mu_1' = \text{Tr}(K) = 0.9477$, $\mu_2' = \text{In}(K) = 0.0521$ and $\mu_3' = \text{Fu}(K) = 0.0002$ (Table 2). The s_i values are estimated based on the method by Bengtsson and Bodmer (1976b) by using the frequencies of *de novo* and parental origin of each chromosomal mutation shown in Table 2. The results are $s_1 = 10/(10+28) = 0.2632$, $s_3 = 3/(3+38) = 0.0732$. As there is no data for *de novo* inversion, we assume $s_2 = s_3$. This assumption may not be far from the truth, because their effective rates are theoretically in the same range, i.e., $Q_{c1' \rightarrow f}(\text{In}) = \text{In}(c1')/2$ and $Q_{c1' \rightarrow f}(\text{Fu}) = \text{Fu}(c1')/2$ (Table 7, also see APPENDIX A). If so, $s_2 = 0.0732$ in the present case. From formula B6, we have $\text{Fu}(nb) = 0.0006$.

In the case of a small population such as wild mice, random sampling drift may fix a particular type of rearrangement. The fixation probability U was studied by Lande (1979). We here reproduce the approximate formula

$$U \cong \frac{1}{N_a} e^{-N_e s} \sqrt{N_e s / \pi} \quad \text{for } N_e s > 2 \quad \text{B7}$$

where N_e and N_a are the effective and actual numbers, respectively, of breeding adults in a population.

In connection with this, it is well known in population genetics that in a small population such as $N_e < 1/s$ mutations can be fixed as if neutral (Crow and Kimura, 1970). The s value of centric fusion (s_3) is estimated here based on the rates of non-disjunction at MII in male mice heterozygous for a single centric fusion (Gropp *et al.*, 1982), i.e., $s_3 = 0.02 \sim 0.26$. To account for the observed fixation of a centric fusion in a wild mouse population, N_e must be smaller than 4~50. On the other hand, as the s value of reciprocal translocation (s_1) is theoretically 0.5, and if we use an estimate of N_e above, $N_e s_1 = 2 \sim 25$, so that if $N_a = N_e$, U ranges from 8×10^{-13} to 0.03. This means that reciprocal translocation is hard to be fixed even in such a small population.

In spite of the well established interpretation mentioned above, there are some experimental data suggesting an alternative possibility. According to Gropp *et al.* (1982), the rate of non-modal MII (i.e., unbalanced types) is 34~61% in oocytes of heterozygotes for a single centric fusion, i.e., $s_3 = 0.34 \sim 0.61$. As the s_3 values are almost comparable with that of reciprocal translocation, it seems difficult to assume such an extraordinary stability of centric fusion for selection. The case of inversion is also problematic. As suggested in APPENDIX A, $s_2 = s_3$ and $\ln(K) = 0.0527 \gg Fu(K) = 0.0006$ in mouse (Table 3), inversion is more likely to be fixed than centric fusion. This expectation is, however, quite opposite to the cytological evidence that no inversion has been observed in wild mouse populations (e.g., Winking, 1986).

We assumed random appearance of chromosomal mutations in the above arguments, and then we had a fundamental problem. One approach for solving such a problem may be to propose an alternative possibility, that centric fusion would occur more frequently than that of reciprocal translocation or inversion in mouse as well as in human newborn babies. This is the main subject we discuss in the present text.

APPENDIX C

Estimation of interactions of acrocentric chromosomes under the hammock structure

We followed the Monte Carlo simulation method used by Imai *et al.* (1986). Let the nucleus of pachytene be a sphere of radius r (Fig. 9). Let i and j be two randomly chosen acrocentric chromosomes from a given haploid karyotype with chromosome number n , and let C_i and C_j be their respective size (a percentage against the total chromosome length of the haploid set). Let the one end of each acrocentric be placed randomly on the inside surface of the sphere which is defined $r' = r \sin(\theta/2)$, where r' is the radius of the area and θ is an angle at the center of the sphere. The other end of each acrocentric is located randomly in the area $D_i \leq C_i$ and $D_j \leq C_j$, where D_i and D_j are distances between the two terminals in chromosomes i and j .

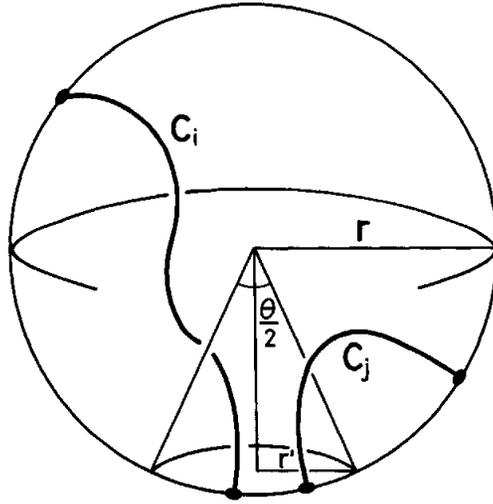


Fig. 9. A schematic representation for estimating the effect of the hammock structure affecting the occurrence probability of reciprocal translocation in an acrocentric karyotype.

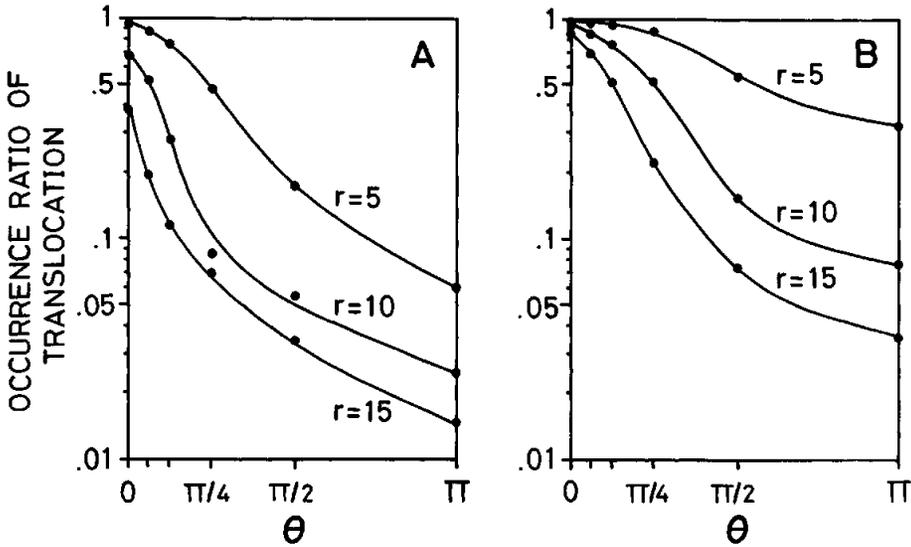


Fig. 10. Effects of nuclear volume and physical proximity of acrocentric chromosomes influencing the probability of the occurrence of reciprocal translocation in man (A) and mouse (B).

Now we ask whether two acrocentrics are close enough to come into physical contact. We assume that if two acrocentrics contact (interact) they exchange their arms at the point of contact (i.e., reciprocal translocation). The relative occurrence of such physical contacts is regarded as the expected probability of reciprocal translocation per a pair of acrocentrics. The estimations were made

with the parameters $\theta = \pi, \pi/2, \pi/4, \pi/8, \pi/16, 0$ and $r = 5, 10,$ and 15 . The results are summarized in Fig. 10. It is a noteworthy characteristic that in both man (Fig. 10A) and mouse (Fig. 10B) karyotypes the frequency of reciprocal translocation in acrocentrics increases as reducing r' in terms of θ values.