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Review Articles

Arrangement of Chromatin in the Nucleus

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Summary. The factors responsible for producing some degree of order to the arrangement of chromatin in the nucleus are reviewed. They are the following: *1.* Chromosomes are attached to the nuclear membrane, nucleolus and intranuclear matrix. As a result they have a relatively fixed position in the nucleus. *2.* In some species somatic pairing results in alignment of homologs. This is rare in mammals. *3.* The association of ribosomal DNA and 5S DNA with the nucleolous results in the close approximation of the chromosomes carrying these DNA sequences. In man and other animals the most obvious consequence is satellite association. *4.* Heterochromatin is condensed onto the inner nuclear membrane and periphery of the nucleolous while genetically active chromatin occupies the more central portion of the nucleus. The results is a peripheral location of late replicating DNA and a central location of early relicating DNA. *5.* The DNA replication points tend to be associated with the nuclear matrix. Autoradiography of briefly labelled cells shows a high frequency of grains associated with nuclear matrix material. *6.* Heterochromatin association results in chromocenters and ectopic pairing. *7.* In addition to all these is the Rabl orientation or alignment of centromeres with centromeres and telomeres with telomeres. This polarization of the chromosomes results from the traction on the centromeres by the spindle fibers. There is no firm evidence for any higher degrees of order that might bring specific functioning genes into close proximity.

Introduction

It is a part of man to attempt to discern order in apparent disorder. In an earlier attempt to do this to the tangle of chromatin in the interphase nucleus a number of possible levels of order were suggested (Comings, 1968). *1.* chromatin was fixed by attachment at multiple sites to the nuclear membrane. *2.* DNA replication took place at the sites of this attachment. *3.* Homologous chromosomes tend to be paired in somatic nuclei, and *4.* Some chromosomes may maintain a non-random orientation in the nucleus. This review will examine the status of these possibilities 11 years later.

Attachment of Chromatin to the Nuclear Matrix

With regards to attachment of chromatin to the nuclear membrane, the idea remains the same, just the terms have changed. The concept of a set of residual nuclear proteins remaining after the DNA has been extracted with high salt solutions began with the very earliest studies of chromatin by Mirsky and Ris (1947). In recent years this concept was refined by the report of Berezney and Coffey (1974) of a nuclear protein matrix or nuclear matrix. When nuclei were gently washed several times with 2 M NaCl the chromatin could be extracted and there remained an elaborate structure containing the nuclear membrane, nucleolar matrix and intranuclear matrix. Examination of this matrix structure after the DNA is only partially extracted indicated chromatin is attached at multiple sites to all three portions of the matrix (Berezney and Coffey, 1976; Comings and Okada, 1976). Thus, while much chromatin is attached to the inner nuclear membrane or lamina (Aaronson and Blobel, 1975), a greater amount is attached to the intranuclear portions of the matrix. If the gently extracted DNA is examined by water spreading and electron microscopy multiple supercoiled domains of DNA are seen which are held in loops by portions of the intranuclear matrix (Comings and Okada, 1976). Similar domains of supercoiled DNA

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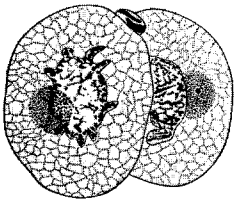
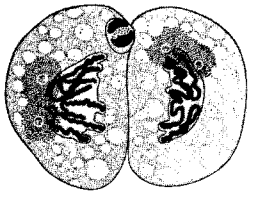
have been demonstrated by other techniques (Cook and Brazell, 1975; Benyajati and Worcel, 1976; Hartwig, 1978). In the study by Ide et al. (1975) it was concluded the supercoiling was organized by a nonhistone protein with a molecular weight similar to the major matrix protein. When the DNA binding characteristics of the nuclear matrix proteins are examined by DNA filter binding techniques they appear to preferentially bind to AT-rich DNA (Comings and Wallack, 1978). Since the G-bands or chromosomes are significantly enriched in AT-rich DNA (Weisblum and deHaseth, 1972; Comings, 1978) this raises the possibility that the chromomeres are held together by virtue of their attachment to pieces of nuclear matrix protein.

This attachment of chromosomes to an architectural superstructure of the nucleus explains some observations of Boveri based on examination of *Ascaris* egs (Boveri, 1888; Wilson, 1925). He showed that chromosomes maintain relatively fixed positions in the nucleus and remain as discrete entities throughout interphase. The *Ascaris* egg nuclei show a number of lobe-like projections which are formed during telophase by the free ends of the V-shaped chromosomes.



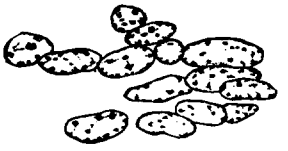
In the following prophase the chromosomes reappear with their ends still lying in these lobes.



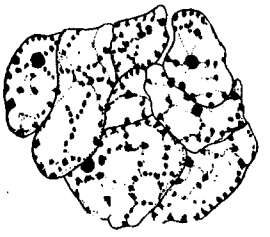
By observing the eggs during a complete cell cycle Boveri demonstrated that the same chromosomes that started in a lobe in telophase ended in a lobe in prophase.

Taken to an extreme the positioning of chromosome lobes would result in each chromosome having its own individual nucleus. This was described by Richards (1917) and Wilson (1925) in the cleavage divisions of the fish *Fundulus.* Here the anaphase chromosomes,

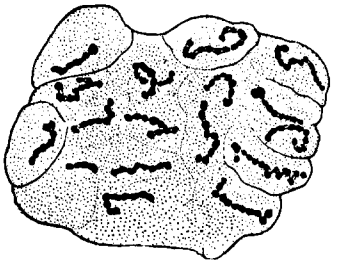
progressively contract into karyomeres,



and form multinuclei.



At prophase the chromosomes are condensed within their karyomeres.



Similar observations have been reported in many organisms (Richards, 1917). In the mite *Pediculopis* (Wilson, 1925) there is an individual spindle apparatus with mitosis taking place inside each vesicle, a process termed *merokinesis.*

More recently, Stack et al. (1977), Brown et al. (1979) and Murray and Davies (1979) have shown that plant (*Allium cepa, Ornithogalum virens*) amphibian (*Triturus cristatus*) and mammalian (*Muntiacus manjak*) chromosomes exist as only slightly decondensed entities in interphase nuclei.

DNA Replication at Matrix Attachment Sites

On the basis of the localization of grains to the nuclear periphery after the presumptive synchronization of cells to the beginning of S phase by amethopterin, it was suggested that DNA replication forks were localized to the site of attachment of chromatin at the nuclear membrane (Comings and Kakufuda, 1968). However, subsequent studies have shown that some replication of DNA can continue in the presence of amethopterin and we now know that this peripheral labeling holds only for late replicating DNA (Williams and Ockey, 1971; Ockey, 1972; Haberman, Tasi and Deid, 1972; Comings and Okada, 1973). Studies of Holmquist and Steffensen

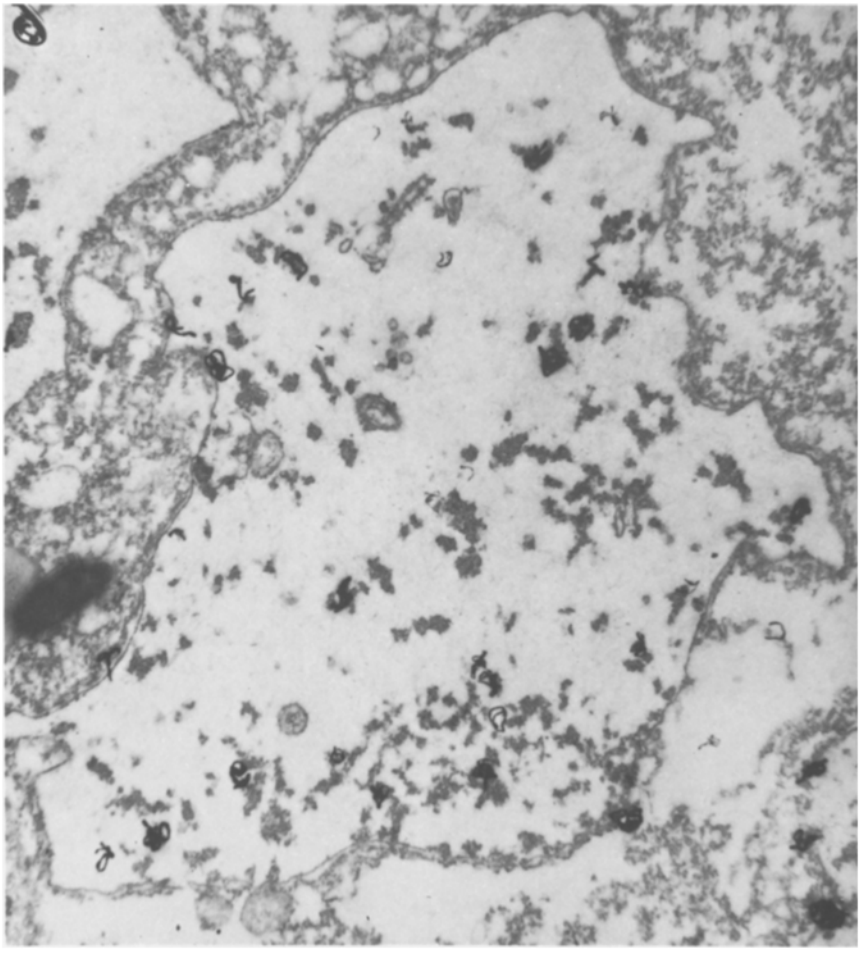


Fig. 1. EM autoradiography of mouse Krebs ascites cells labeled with ^{3}H-thymidine (10 μCi/ml) in McCoy's modified media for 10 min, showing the association of grains with the nuclear matrix (see text). After labeling isolated nuclei were washed once in 0.25 M sucrose, 50 mM Tris, pH 7.4, 5 mM $MgCl_2$, then once in 2 M NaCl, 10 mM Tris, 0.2 mM $MgCl_2$, pH 7.5, fixed in 3% glutaraldehyde, 1% osmic acid, embedded, sectioned and autoradiographed. (From D. E. Comings and T. A. Okada, unpublished material.) (10,000×)

(unpublished) show that in *Drosophila* salivary gland nuclei the late replicating bands are membrane or nucleolus associated. The possibility that the DNA replication point in mammals is in fact localized to the attachment site of chromatin to matrix has been reintroduced by studies of Berenzney and Coffey (1975). Much of the newly replicating DNA is associated with the nuclear matrix. This has been confirmed by others (Dijkwel et al., 1979). We have attempted to verify the association of newly replicating DNA with the nuclear matrix by EM autoradiography. However, the intranuclear matrix is so extensively dispersed throughout the nucleus it was difficult to find matrix free areas as a control (Okada and Comings, unpublished observations). There were unquestionably many instances of grains at DNA-matrix interface (Fig. 1).

A second major group of structures associated with the nuclear matrix are the heterogenous nuclear RNA (HnRNA) and heterogenous nuclear ribonucleoprotein (HnRNP) complexes (Miller et al., 1978). We have verified this by two dimensional gel electrophoresis of the nuclear matrix proteins. They contain all the same classes of proteins found in the purified HnRNP particles (Comings et al., 1980). We also find that the nuclear membrane, nucleolar matrix and intranuclear matrix are composed of relatively distinct sets of proteins.

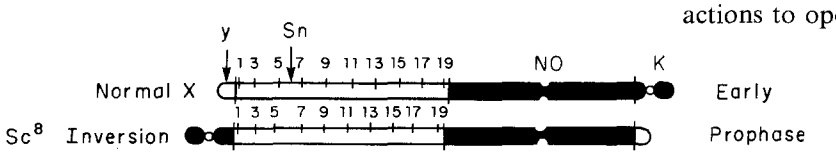
Combining all of this evidence one can say that the genetically inactive late replicating DNA is condensed onto the undersurface of the inner nuclear membrane and nuclear lamina and around the nucleolus, while the genetically active DNA is centrally located, attached to the intranuclear matrix where it is also associated with a network of HnRNP particles. Whether the DNA composition (or sequence) or some aspect of the matrix proteins determines the attachment sites remains to be determined.

Somatic Pairing of Homologous Chromosomes

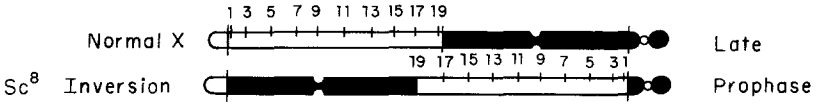
In the Diptera this is well documented. In *Drosophila* the somatic pairing that is present during interphase may be destroyed at metaphase by superimposed realignment of chromosomes on the spindle. This was

illustrated by Becker (1969) who examined *Drosophila* heterozygous for long paracentric inversions.

In early prophase the normal X- and the Sc^8 inversion were homologously paired along most of their length.



Later in prophase the Sc^8 rotated 180° so that both centromeres were together toward the center of the metaphase plate.



Hinton (1947) observed somatic pairing of homologous regions in prophase of *Drosophila* heterozygous for X-2L translocations and noted that pairing began at a time when the chromosomes were separated by distances too great for short distance chemical interactions to operate.

Table 1. Somatic and premeiotic pairing in plants

Species	Comment	Reference
Yucca (many species)		Müller, 1909; Watkins, 1935
Oenothera lata (primrose)		Gates, 1912
Morus indica L. (mulberry)		Tahara, 1910
Oryza sativa (rice)		Kuwada, 1910
Liliaceae	Many species	Watkins, 1935
Dahlia	Secondary association of homeologous bivalents	Lawrence, 1931
Haplopappus gracilis	$2n=4$ (dicot)	Mitra and Steward, 1961; Brown and Stack, 1968
Rheo discolor	$2n=12$ (monocot). Complex heterozygote with ring formation in somatic cells clearly indicating somatic pairing	Brown and Stack, 1968
Plantago ovata and insularis	$2n=8$	Ashley, 1976; Stack and Brown, 1969a
Ornithogalum virens and Sp	$2n=6$	Stack, 1971; Therman, 1951; Godin and Stack, 1976
Avena sativa L. (oats)	Non-homologues random, homologues tendency to pairing (no. 21 and a telocentric pair). Less somatic pairing with an asynaptic genome	Thomas, 1973
	Somatic pairing	Sadasivaiah et al., 1969; Dubuc and McGinnis, 1970
	No somatic pairing	Dvorak and Knott, 1973
Hordeum vulgare L. (Barley)	Somatic pairing with cold treatment	Fedak and Helgason, 1970
	Somatic pairing increased with chloramphenicol and colchicine treatment	Yoshida and Yamoguchi, 1973
Zea maize	Heterochromatic knobs of homologous chromosomes closer together in premeiotic interphase than non-homologous knobs	Maguire, 1967, 1972
	No evidence for pre-meiotic pairing	Palmer, 1971
Secale cereale (rye)	Homologous pairing of rye chromocenters in interphase nuclei in wheat-rye addition lines	Singh et al., 1976
Triticium aestivum (common wheat)	Somatic pairing	Feldman et al., 1966, 1972
	No evidence for pairing	Dvorak and Knott, 1973; Darvey and Driscoll, 19
Impatiens balsamina	Close association of homologous centromeres in premeiotic interphase	Chauhan and Abel, 1968

Table 1 (continued)

Species	Comment	Reference
Salvia nemorosa (scarlet sage)	Close association of homologous centromeres in pre-meiotic interphase	Chauhan and Abel, 1968
Crepis capillaris	Somatic pairing and polarization of chromosomes	Kitani, 1963; Ferrer and Lacadena, 1977
	Random arrangement in somatic metaphase	Matsuura, 1937
Arabidopsis thaliana	Somatic pairing	Steinitz-Sears, 1963; Hironi and Redei, 1965
Angiosperms	Somatic pairing in 33 species, 29 genera and 15 families of angiosperms	Watkins, 1935
Daphne odora	Somatic pairing	Hiraoka, 1958
Tragopogon Sp (composite)	Premeiotic pairing	Scherz, 1957
Lilium longiflorum	No premeiotic pairing	Walters, 1970
Lycopersicon	Suggested premeiotic interphase pairing → pachytene pairing → post-pachytene separation at "zygotene"	Moens, 1964

Many plants also show good evidence for somatic pairing, although negative reports abound (Table 1). The evidence for somatic pairing is poorest in mammals. Studies of the Indian Muntjak are a good example. An early study suggested somatic pairing was present (Heneen and Nichols, 1972) but most show it is not (Cohen et al., 1972; Nur, 1973; Korf and Diacumakos, 1977). Studies of banded chromosome spreads in humans show no evidence for homologous pairing (Sele et al., 1977). Because of the potential disruption of somatic pairing by the spindle fibers, as well illustrated in the studies of scute[8] in *Drosophila*, the most accurate assessment of interphase chromosome positions would be a procedure that would mark a given part of the nucleus then allow visualization of portions of metaphase chromosomes that were near that mark. Microbeam U.V. irradiation of interphase nuclei followed by examination at mitosis for chromosomal sites of unscheduled DNA synthesis allows this to be done. Preliminary studies do not support the presence of somatic pairing in Chinese hamster cells (Cremer et al., 1979; Zorn et al., 1979). They also support the concept of interphase chromosomes occupying only a small portion of the nucleus and not changing this position during the cell cycle.

Several studies have reported more impressive evidence for somatic pairing in pre-meiotic metaphases (McDermott, 1971; Jericek, 1975). Here it could play an obvious role in preparing the cell for meiotic pairing (Comings and Okada, 1970).

Factors which Produce a Partial Ordering of Nuclear Chromatin

While the evidence for a non-random association of all chromosomes is extremely limited (Costello, 1970; Ford and Wilson, 1972), there are a number of influences which interpose some degree of order to the nuclear chromatin. These are listed in Table 2 and the reports of some of these effects on human chromosome are shown in Table 3.

Item 1. Chromosomes attached to the nuclear matrix and

2. Somatic pairing, and discussed above.

3. Ribosomal DNA associated with nucleolus. The number of nucleoli in a nucleus is often much less than

Table 2. Factors which produce a partial ordering of nuclear chromatin

1. Chromosomes are attached to the nuclear membrane, nucleolous, and intra-nuclear matrix.
   → fixed positions of chromosomes in the nucleus
2. Somatic pairing (in some species)
   → alignment of homologs
3. Ribosomal DNA associated with the nucleolous
   → satellite association
4. 5S DNA associated with the nucleolous
   → 5S DNA chromosome site close to nucleolous organizers
5. Heterochromatin condensed onto nuclear membrane and periphery of nucleolous
   → late replicating DNA peripheral, early replicating DNA central
6. Heterochromatin association, chromocenters and ectopic pairing
   → association of heterochromatic regions
7. Rabl orientation and bouquet formation
   → centromeres at nuclear membrane, telomeres at opposite nuclear membrane
   → chromosome arms acutely flexed at centromere
   → polarization of chromosomes

Table 3. Mechanisms and types of chromosome association in human cells

I. *Nucleolus Association*	
Satellite association	Ferguson-Smith and Handmaker, 1961, 1968; Harden, 1961; Ohno et al., 1961
Non-random	Hens et al., 1975; Cooke, 1971; Patil and Lubs, 1971
Random	Shaw et al., 1969; Jacobs et al., 1976
Satellited chromosomes associated with other 2° constrictions on no. 2, 6, 18, 21/22	Ferguson-Smith and Handmaker, 1963; Shaw, 1961; Ros, 1968
Giemsa 11 positive heterochromatin of chromosome no. 9 associated with nucleoli in somatic cells and with parameres (Hungerford et al., 1972) in pachytene cells	Gange et al., 1973
Y chromosome associated with the nucleolus	Bobrow et al., 1971; Gange et al., 1972; Wyandt and Iorio, 1973; Goldgefter et al., 1973
1q42–44 with 5S DNA locus is associated with the nucleolus	Steffensen et al., 1974
II. *Somatic Pairing*	
Somatic pairing of 1, 2, 3, and 16	Schneiderman and Smith, 1962; Chandra et al., 1972
1, 2 and 3 not paired	Merrington and Penrose, 1964
Concordant bending of homologous chromosomes suggesting somatic pairing	Groop and Odunjo, 1963
Pre-meiotic pairing in spermatogonia	McDermott, 1971
No-somatic pairing	Sele et al., 1977
III. *Heterochromatin at Nuclear Membrane*	
Late replicating chromosomes peripheral	Ockey, 1969
X and Y peripheral	Morishima et al., 1963; Miller et al., 1963a; Barton et al., 1964; Ockey, 1969; Galperin, 1969; Chandra et al., 1972; Hoehn and Martin, 1973
Y not peripheral	Spence et al., 1973; Tishler et al., 1974
13, 17–18, 21 peripheral	Miller et al., 1963b
1h heterochromatin not at nuclear membrane	Hoehn and Martin, 1973
IV. *Chromosome Size*	
Larger chromosomes more peripheral than smaller ones	Hoo and Cramer, 1971
V. *Non-specific Association of Heterochromatin*	
Association of Y and 1h	Hoehn and Martin, 1973

the number of nucleolus organizers indicating nucleoli often fuse. This draws together nucleolus organizing chromosomes to produce satellite association (Ohno et al., 1961).

4. 5S DNA associated with the nucleolus. 5S RNA is involved in ribosome formation and the 5S DNA is nucleolar associated. This brings the chromosome carrying these genes into close association with each other (Pardue et al., 1973) with the nucleolus and the satellited chromosomes (Steffensen et al., 1974, 1977).

5. Heterochromatin is condensed onto the nuclear membrane and nucleolus. This well established location of heterochromatin means that the heterochromatin will occupy a defined position in the nucleus relative to the euchromatin. As a result, predominately heterochromatic chromosomes, such as the inactive X-chromosome, will tend to occupy a peripheral position in the metaphase spread. Some suggest the Y is also peripheral while others disagree (Table 3).

6. Heterochromatin association, chromocenters and ectopic pairing.

The intimate association of the heterochromatin of *Drosophila* salivary gland polytene chromosomes to form the chromocenters is well known. Similar but less consistent association of hetereochromatin occurs in most species. The degree of association of mouse centromeric heterochromatin into chromocenters varies from tissue to tissue (Hsu et al., 1971). The content highly repetitious satellite DNA in the intercalary heterochromatin is a factor in its ability to undergo "ectopic pairing" (Barr and Ellison, 1972). Association of heterochromatin regions occurs to a lesser degree in

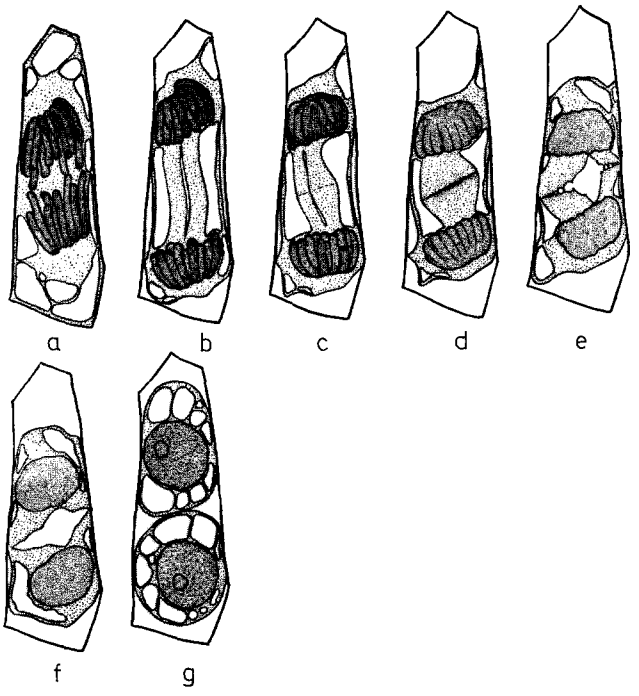


Fig. 2. Example of the Rabl orientation of chromosomes as seen in the cell cycle of *Tradescantia* (Belar, 1928). At anaphase the chromosomes are polarized by the traction from the spindle apparatus. In telophase they retain this orientation of centromeres at one side of the nucleus, chromosome folded sharply at the centromere and telomeres at the opposite side of the nucleus. The general orientation persists despite descondensation of some of the chromatin in interphase

human cells (Schmid et al., 1975) and accounts for some of the non-random associations of chromosomes on the metaphase plate (Shaw, 1961; Ferguson-Smith and Handmaker, 1963; Khan and Martin, 1967).

7. Polarization of chromosomes and the Rabl orientation.

Polarization of chromosomes refers to an alignment of the chromosomes with the centromeres grouped together at one part of the nucleus with the telomeres at the opposite side of the nucleus. The earliest description of this was by Rabl in 1885. In his report the centromeres was grouped near the centriole, the chromosome arms were parallel and attached by the telomeres to the opposite side of the nucleus. This is referred to as the *Rabl orientation* (Gelei, 1921, 1922). It becomes established in the last mitotic telophase prior to meiosis. Such an orientation may be a prerequisite to orderly meiotic pairing (Smith, 1942).

A similar orientation, frequently seen in leptotene and zygotene, is termed the *bouquet formation.* This orientation is usually lost in early pachytene with the chromosome ends assuming a random arrangement in the nucleus. In some organisms such as the mantid, the bouquet once again re-forms in mid to late pachytene (Hughes-Schrader, 1943). This indicates the bouquet "cannot be interpreted simply as a passive relic of previous telophase (Rabl) orientation, but involves an active orientation of the chromosomes" (Hughes-Schrader, 1943).

Rabl type polarization need not be restricted to premeiotic cells. On the basis of cytological evidence it has been reported in many organisms such as *Tradescantia* (Belar, 1928) (Fig. 2); Liliaceous plants (Smith, 1942; Smith and Boothroyd, 1942), *Allium cepa* (Stack and Clarke, 1974; Kitani, 1963; Vanderlyn, 1948; Fussell, 1975); *anopheles* (Diaz and Lewis, 1975); and *Drosophila* (Oksala, 1958). The use of autoradiography to identify the late labeling centromeres and telomeres of onion tip nuclei indicates the centromeres are grouped together at a nuclear membrane associated chromocenter at one side of the nucleus and the telomeres are scattered in an arc at the other side (Fussell, 1975).

Non-Random Translocations

An obvious means of testing the possibility that chromosomes bear a non-random relationship to each other is to examine chromosomes involved in reciprocal translocations. Are they random or do certain chromosome sites show a preference to combine with certain others.

Some deviations from random expectation are reported in studies of breakpoints of human translocations (Obe, 1969; Nakagome and Chiyo, 1976; Aurias et al., 1978). Most striking is a predelection for involvement of centromeres and telomeres with a relative sparing of the middle of the arms. Other than certain special cases such as 14/21 translocations (Hecht et al., 1968; Hecht and Kimberling, 1971) and the Philadelphia 21/9 translocation in chronic myelogenous leukemia (Rowley, 1973), there is no evidence for preferential involvement of specific chromosomes in human translocations.

In certain diseases such as Bloom's syndrome, and after treatment of cells with agents like mitomycin C, there is a striking frequency of interchanges between homologous chromosomes. This suggests that somatic pairing is present during all or some part of the cell cycle (Vogel and Schroeder, 1974). Given the relative paucity of firm evidence for somatic pairing in mammalian cells an alternative explanation is that during the repair of these lesions fairly long regions of single stranded whiskers are produced and base pairing and exchange can occur when by chance a comparable whisker on a homologous chromosome is encountered (Comings, 1975). The absence of exchange between homologs with other types of clastogens and in other

diseases which result in increased breakage (where long whiskers are presumably not produced), favors this interpretations.

Jancey and Walden (1972) examined the data based on 1003 reciprocal translocations and 60 inversions in maize and the data available from *Drosophila* (Lindsley and Grell, 1968). There was a greater than expected frequency of breakage in or near the centromere. After correction for this other non-random distributions were found in maize. Further analysis (Walden, unpublished), showed a high frequency of reunions for breaks which were on different chromosomes but at similar distances from their centromeres. This supports a Rabl type of interphase organization with the centromeres clustered together at one part of the nuclear membrane and the telomeres at the opposite part of the cell. Studies of breakage and reunion in other systems also provides strong evidence for polarization of somatic cell chromosomes (Kur and Natarajan, 1966; Sax, 1940; Evans, 1961; Evans and Bigger, 1961).

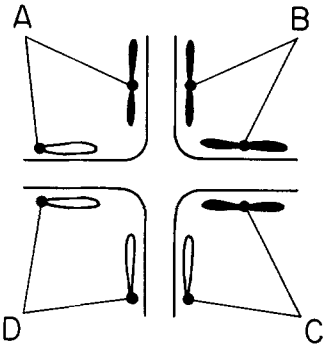
Telomeric Association of Chromosomes

Wagenaar (1969) has suggested that the chromosomes of several plants are attached to each other by their telomeres to form tandom associations. Specific end-to-end associations have also been observed in *Drosophila* (Hinton and Atwood, 1941; Kaufman and Gay, 1969), and in general organisms which have blocks of constitutive heterochromatin at the telomeres show telomeric associations of that heterochromatin. In locusts where the chromosomes can be identified, the associations were non-homologous and random (Drets and Stell, 1974).

Somatic Reduction and Segregation of Haploid Genomes

Further evidence that chromosomes are not randomly arranged in the nucleus comes from the observation that under certain circumstances diploid or polyploid somatic cells can segregate out haploid or near haploid genomes. Such *somatic reduction* may occur by *1.* multipolar divisions (Huskins, 1948; Allen et al., 1950; Pera and Schwarzacher, 1969), *2.* division without chromosome duplication (Huskins, 1948a; Grell, 1946; Storey, 1968), *3.* chromosome elimination or *4.* tight somatic pairing of chromosomes (Yoshida and Yamaguchi, 1973). The latter may also mimic somatic reduction (Boss, 1955). The following are some examples.

1. Hybrids of Cattle and Mink Cells. When diploid cells of cattle ($2n = 60$) with telocentric chromosomes, and mink ($2n = 30$), with metacentric chromosomes, were grown together some hybrid cells containing a haploid complement of each species ($n = 45$) were produced (Teplitz et al., 1968). After exposure of these hybrid cells to room temperature they reverted to parental type cells within 72 h, indicating a segregation of complete sets of chromosomes. The most likely mechanism for these phenomena is that the hybrid cells arose from fusion of two parental cells followed by a tetrapolar mitosis in which half of the daughter cells (A and C) would be hybrids.



As long as these cells remained "diploid" the hybrid cells would be maintained. However, induction of tetraploidy by exposure to room temperature would again allow a tetraploid mitosis with production of parental types (B and D). This implies a positioning of chromosomes on the equatorial plate of somatic cells that allows separation of haploid genomes.

Further evidence that this is the manner of segregation was demonstrated by studies of binucleate rat kangaroo cells in which the nuclei were found to be incompletely synchronous. After exposure to ^{3}H-thymidine there were some cells with only one nucleus labeled, and some with one well labeled and the other lightly labeled (Heneen, 1971). Both nuclei entered mitosis simultaneously giving a tetrapolar mitosis. Autoradiography showed that the parental genome was distributed on two adjacent arms of the + shaped equatorial plate. The four daughter nuclei thus represented two parental and two recombinant types. The labeling pattern in the recombinant nuclei, showing one half of a nucleus labeled and the other half unlabeled, indicated the chromosomes maintained their positions during interphase.

2. Recombinant Diploids from Tetraploid Human Cell. Martin and Sprague (1969) cultured fibroblasts from a patient heterozygous for chromosome 16 with an unusually long arm (16/16q+). Spontaneous tetraploid cells were cloned and examined through several passages. Among these cells, 3–17% reverted to diploidy. Examination of these indicated that 17% were non-recombinant parental type (16/16q+) while the rest were recombinant with 10% 16/16 and 15% 16q+/16q+. As described above, such recombinant types would be expected after a tetrapolar mitosis.

Chromosome recombination was also seen in other types of heterozygous fibroblasts but in two tetraploid XXYY cells no XX or YY recombinants were seen (Martin and Sprague, 1969). This is consistent with Ohno's failure to find somatic segregation of sex chromosomes in deer mice or fish (Ohno, 1966). In chimeric cattle recombination of red cell markers has been reported (Stone, 1964).

3. Tripolar Mitoses in Microtus agrestis. By using Feulgen stained kidney epithelial cells of *Microtus agrestis* Pera and Schwarzacher (1968) noted the presence of both diploid tripolar mitoses (4C) and tetraploid tripolar mitoses (8C). The diploid tripolar mitoses produced one diploid daughter nucleus and two haploid daughter nuclei. Most tetraploid mitoses divided into one diploid daughter nuclei and two triploid daughter nuclei (3C). In two cases tripolar tetraploid mitoses led to one haploid, one diploid, and one tetraploid daughter nuclei.

Further studies with chromosome banding proved that true haploid sets of chromosomes were being segregated (Pera and Rainer, 1973). Similar results have been obtained with banding of Rhesus monkey cells (Palitti and Rizzoni, 1972); Rizzoni et al., 1974). This would explain the occasional observation of near haploid cells in mammalian peripheral blood (Sinha, 1967) and in diploid-triploid chimeric frog (Volpe and Early, 1970).

The banding studies do not answer the question of whether there is random segregation of the chromosomes as in meiosis thus producing a true parasexual cycle, or whether maternal and paternal sets are segregating. Until proven otherwise, the latter seems most likely.

4. Somatic Reduction in Insects and Plants. In some organisms, especially insects, haploid sets of chromosomes are eliminated during development. A particularly impressive example is seen in the maturation divisions of weevil eggs of the tetraploid species *Otiorrhynehus dubius.* Here four types of metaphase plates could be distinguished (Suomalainen, 1940). a. One group of 44 chromosomes, b. One group of 33 chromosomes and a second group of 11, c. Two groups of 22 each, and d. three groups of 22, 11 and 11 chromosomes. This indicated that haploid sets were probably being kept together.

In plants somatic reduction has frequently been reported (Huskins, 1940a, b; Huskins and Chen, 1950; Wilson and Cheng, 1949; Storey, 1968; Lesins and Sadasivaiah, 1973; Yoshida and Yamaguchi, 1973), and has occasionally been called *somatic meiosis* (Huskins, 1940a). Both cytological evidence and the production of haploid mutants (Ross, 1962; Chen and Ross, 1963; Simantel and Ross, 1963a, b) imply segregation into haploid sets of chromosomes.

Conclusion

The types of order discussed above are the natural consequences of certain physiological functions of the genes and chromosomes. The ribosomal and 5S genes will hover together as they conger up the nucleolus. Since chromosomes are attached to the nuclear membrane, nucleolus and nuclear matrix, the condensed chromatin (heterochromatin) will crowd closer to these structures than the decondensed active chromatin. Ectopic pairing of heterochromatin will add to this tendency to cluster together. Finally, like a steam press rolling over all this is the Rabl orientation due to the spindle apparatus lining up centromeres at one end of the nucleus and the telomeres at the other. Unfortunately, for those who would like to see even more order, so genes might by their proximity show some functional cooperation, the evidence is meager to non-existent. The best evidence against such cooperation is the normal function of genes on single human chromosomes in human-mouse cell hybrids.

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