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THE LEPTOTENE-ZYGOTENE TRANSITION OF MEIOSIS

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ABSTRACT

The leptotene/zygotene transition of meiosis, as defined by classical cytological studies, is the period when homologous chromosomes, already being discernible individualized entities, begin to be close together or touching over portions of their lengths. This period also includes the bouquet stage: Chromosome ends, which have already become integral components of the inner nuclear membrane, move into a polarized configuration, along with other nuclear envelope components. Chromosome movements, active or passive, also occur. The detailed nature of interhomologue interactions during this period, with special emphasis on the involvement of chromosome ends, and the overall role for meiosis and recombination of chromosome movement and, especially, the bouquet stage are discussed.

I will only remind you that meiosis is still a potential battleground where dead hypotheses litter the field or rest uneasily in shallow graves, ready to emerge and haunt any conscientious scientist who tries to consolidate a victory for any particular thesis.

JH Taylor (280) [From 149]

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INTRODUCTION

Sexually reproducing organisms produce gametes that have half the normal cellular chromosome complement; in consequence, union of male and female gametes restores the normal cellular chromosome complement rather than doubling it. Meiosis is the process that accomplishes the requisite halving via a program in which a single round of DNA replication is followed by two successive rounds of chromosome segregation. A diploid meiotic cell thus yields four haploid meiotic products. During the mitotic cell cycle, in contrast, DNA replication is followed by a single round of chromosome segregation. In most animals, the meiotic products are transformed directly into gametes. In higher plants, they grow by mitotic divisions into gametophytes, which then yield pollen and ovules. In many fungi, bryophytes, and pteridophytes, they constitute the haploid phase of the life cycle.

A Problem of Connection

During mitosis, sister chromatids move to opposite poles (disjoin) in an "equational" segregation pattern. During meiosis I, in contrast, replicated maternal and paternal homologous chromosomes, each comprising a pair of sisters, move to opposite poles in a "reductional" (72) segregation pattern. Sister chromatids

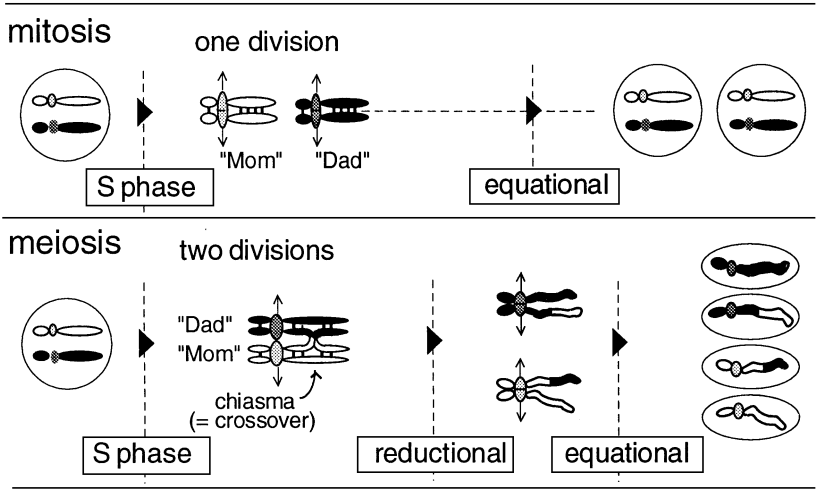


Figure 1 Comparison between mitotic and meiotic divisions.

then segregate equationally at meiosis II. That is, "chromosomes" segregate at meiosis I whereas "chromatids" segregate at meiosis II (Figure 1).

During mitosis, each pair of sister chromatids is intimately connected along their lengths and, in special ways, at the centromere/kinetochore region. These connections ensure bipolar orientation of sisters on the metaphase plate: When spindle fibers are attached to sister kinetochores from different poles, opposing poleward forces create tension at the kinetochore. Once all chromosomes are properly oriented, i.e. under tension, cellular regulatory signals trigger release of sister chromatid connections, first along the chromatid arms and then within centric regions; sister chromatids then move to opposite poles. Poleward movement per se may promote the release of remaining "fortuitous" intersister connections (e.g. topological catenations; 160).

At meiosis I, homologues are connected to one another via the combined effects of two features: one or a few interhomologue crossovers in plus connections between sister chromatids analogous to those present during mitosis (Figure 1). These interhomologue connections are observable cytologically as chiasmata (153). A pair of connected homologues (a "bivalent") can undergo bipolar orientation on the meiosis I spindle via the same mechanism used for orientation of connected sisters during mitosis. Many of the most unique events and aspects of meiosis are devoted to providing this essential interhomologue connection. In particular, crossover recombination is mechanically crucial for meiosis, irrespective of any evolutionary role.

Occurrence of the two meiotic divisions also depends upon the biphasic release of sister chromatid connections, which is analogous to that observed during mitosis except that arm connections and centric connections are lost successively at the two successive meiotic divisions rather than during the single mitotic division (Figure 1). At meiotic anaphase I, cell cycle–regulated sister chromatid connections lapse along the arms but persist in the centric regions. The connection provided by the crossover is thereby released and the two homologue kinetochores move to opposite poles, trailing their associated chromatid arms. Along each chromosome arm, fortuitous intersister connections are released distal to the most centromere-proximal chiasma. At meiosis II, sisters are aligned between the poles at metaphase II via their centric connections. The centric connections then lapse in response to regulatory signals, triggering the onset of anaphase II, loss of residual fortuitous connections, and resultant disjunction of individual chromatids (Figure 1).

The essential equivalence of bipolar homologue alignment and sister separation at meiosis I with the corresponding processes in mitotic cells has been shown directly: If a meiotic bivalent is moved onto a mitotic spindle by micromanipulation, the ensuing round of chromosome segregation is reductional (meiotic) rather than equational (mitotic) (213).

Meiosis and Mendel

The meiotic process provides the physical explanation for Mendel's Laws and for their most important exception, the occurrence of crossing over.

According to Mendel's first law, maternal and paternal versions of any given single allele assort randomly. This behavior is explained because (*a*) each of the gametes resulting from a round of meiosis contains either the paternal or maternal version of a given chromosome region, with the two types represented in equal numbers within the total pool, and (*b*) a zygote is formed by two gametes, each drawn randomly from such a pool. Mendel's second law considers that the alleles for two different traits segregate independently of one another. This finding is explained in a simple way if the genes for the two traits lie on different chromosomes: each bivalent aligns on the meiosis I spindle independently of all other bivalents and, in most cases, without respect to the parental origin of the component chromosomes. If, however, the genes for two traits lie on the same chromosome, the situation is more complex. In this case, the segregation pattern observed depends upon the frequency of crossing over between the two corresponding loci. In the absence of any crossing over, the maternal and paternal alleles of two traits present on the same chromosome will never segregate from one another, precisely the opposite of Mendel's law. In fact, Mendelian segregation will be observed only if there is a very high frequency of crossing

over between the two loci, in which case the four possible combinations of the pairs of alleles (two parental and two recombinant) will occur with equal frequency. When an intermediate amount of crossing over occurs, partial linkage between the two traits will be observed. Indeed, the organization of genetic traits in a linear array and the existence of genetic recombination were inferred from the identification of such exceptions to Mendel's second law (145, 206, 274). For an early account of how meiosis was discovered at the chromosomal level and related to the requirements of genetic segregation, see Darlington (72).

The Stages and Events of Meiosis: Thumbnail Sketch

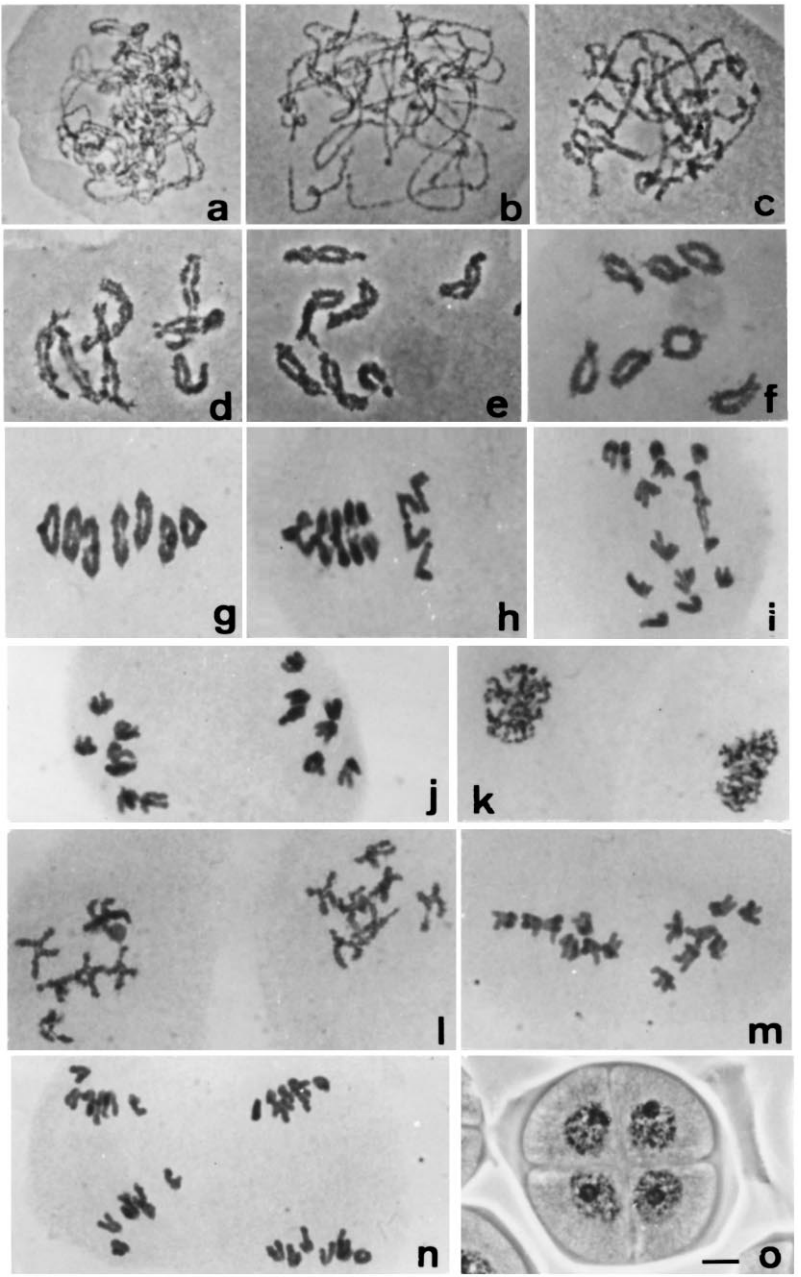
The existence of the meiotic process at the chromosomal level and the definition of its basic stages were mainly elucidated by light microscopy of fixed, stained chromosome preparations (242, 299). Although the process is continuous, stages were shown—originally with hand drawings and later by photographic methods—in terms of a series of changes in the morphology of the chromosomes (Figure 2). Virtually identical stages are found in all organisms (Figures 2 and 3).

Light microscope studies of the mitotic cycle revealed a morphological progression in which unindividualized chromosomes undergo compaction into relatively long and thin entities that become progressively shorter and fatter and finally split into two separated sister chromatids. Arm regions separate prior to centric regions; the separated chromatids first lie side-by-side and then move to opposite poles with evidence of peripheral stickiness. These features have been reemphasized by recent scanning electron micrographic images (117, 275).

Meiotic chromosome morphogenesis, in a very oversimplified sense, is exactly analogous to mitotic chromosome morphogenesis, with only two exceptions: occurrence of interhomologue interactions and discoordinate separation of sister arms and centric regions at the two divisions.

From S-phase through the period when chromosomes are long and thin, interhomologue interactions occur [pairing, recombination, and synaptonemal complex (SC) formation] that juxtapose homologous chromosomes along their lengths with the concomitant formation of one or several crossovers per bivalent. Chromosomes then shorten and thicken as during mid- to late-mitotic prophase. In an early transitional phase, homologues lose the connections along their lengths while retaining crossovers; thus, fully condensed homologues are separated along their lengths and joined only at chiasmata.

Sister chromatids separate along their arms at meiosis I, thus permitting recombinant chromatids to move with their centromeres; centromere cohesion is retained, however, to permit chromosome orientation for meiosis II, at which point it is finally lost and sisters move to opposite poles.



THE CLASSICAL STAGES *Preprophase* The meiotic cycle begins with cells in a premeiotic G1/G0 condition characterized by marked expansion of the nucleus (242; Figure 3*a*). Meiotic S-phase (sometimes called premeiotic S-phase) follows, with concomitant formation of intersister connections. This stage, like its mitotic counterpart, is characterized by diffuse chromatin within which strongly staining foci are often seen (Figure 3*b*,*c*). The molecular events of S-phase in mitotic and meiotic cells are also closely analogous, with the important exception that meiotic S-phase always takes much longer (e.g. 138). In some organisms, homologues are paired at premeiotic G1/G0, in which case pairing may be loosened or lost during meiotic S-phase and then restored (298).

Early to mid-prophase At preleptotene, chromosomes of many organisms undergo a cycle of compaction, which may be more or less pronounced (Figure 3*d*). Next comes the leptotene stage (Greek "leptos" = thin), characterized by chromosomes that are discernibly individualized, appearing thin and thread-like (Figures 2*a* and 3*e–g*). Overall, the total array of chromosomes appears as a dense tangle of such threads, but significant underlying order may already be present. Next comes zygotene (Greek "zygos" = pair), at which stage chromosomes are shorter and fatter, with obvious indications that homologues have begun to come close together. By the next stage, pachytene (Greek "pakhus" = thick), synapsed homologous chromosomes (each comprising a pair of sisters) are shorter and thicker and tightly associated (Figure 2*b–d*).

Chromosome morphogenesis during these stages includes three components (Figure 4): (*a*) establishment of an appropriate relationship between sister chromatids, including development of specialized axial chromosome structure; (*b*) interhomologue interactions, including recognition between intact chromosomes, recombination at the DNA level, and formation of the prominent structure that connects homologue axes, the synaptonemal complex; and (*c*) temporally programmed variations in the molecular composition and compaction status of bulk chromatin and axis-associated components.

Important changes in the three-dimensional (3D) configuration of the chromosomes accompany these events. By late leptotene/early zygotene, chromosomes occur in a compact configuration, a "knot" within which no substructure is visible (Figure 3*i*) and/or in a "bouquet" form in which telomeres are spatially associated and chromosome arms loop outward in a flower-like array

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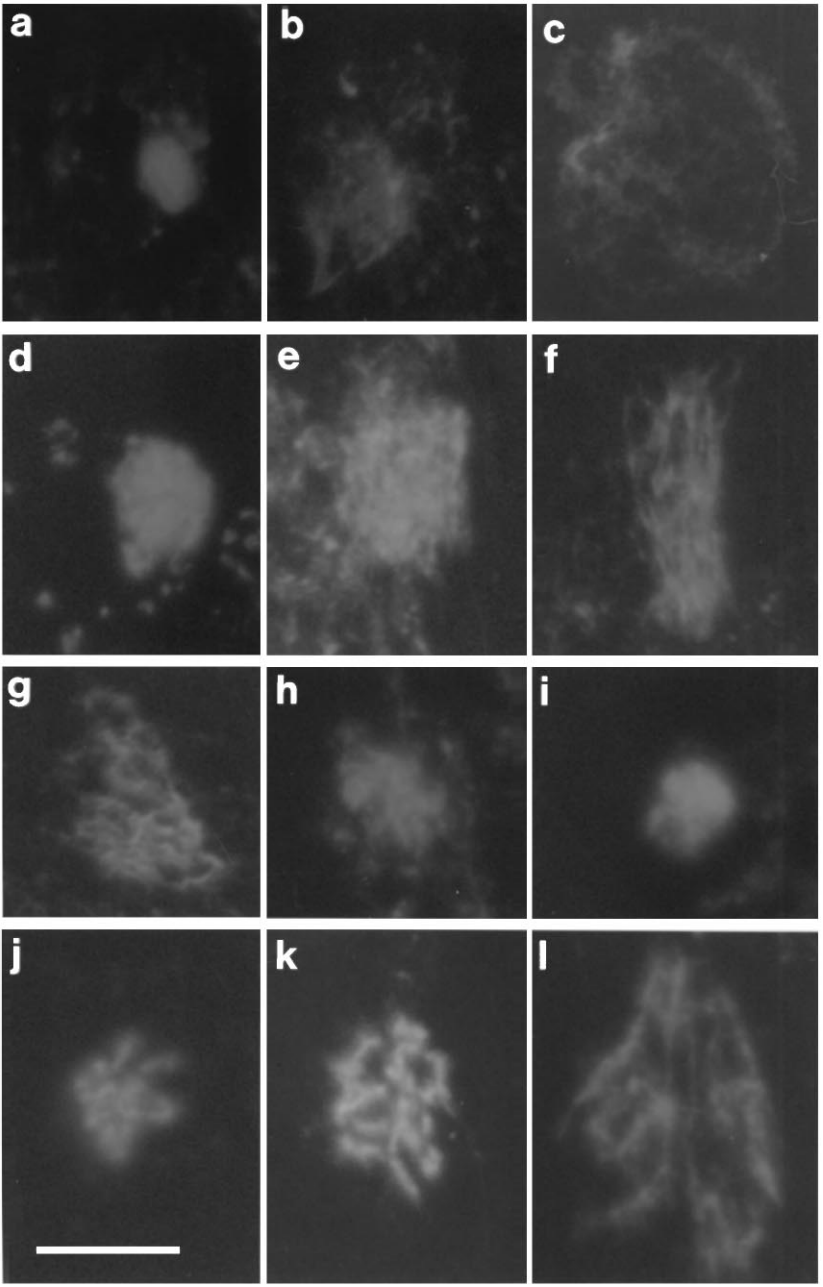
Figure 2 Meiotic divisions I and II in the rye *Secale cereale* microsporocytes. (*a*) Early zygotene; (*b–d*) early to late pachytene; (*e*) diplotene; (*f*) diakinesis; (*g*, *h*) metaphase I; (*i*, *j*) anaphase I; (*k*) telophase I; (*l*) prophase II; (*m*) metaphase II; (*n*) anaphase II; and (*o*) four haploid pollen mother cells. Bar = 5μ. (Photographs by DZ.)



(Figure 3*j*). By the end of pachytene, however, this arrangement is lost and chromosome ends are displayed evenly around the inner surface of the nuclear envelope (Figure 3*k*).

More specifically, each pair of sister chromatids develops into a linear array of loops connected at their bases by a single conjoined structural axis (e.g. 201a); this axis is finally completed by formation of a highly ordered axial structure discernible in ultrastructural analysis as the lateral or axial element. Within this array, the two underlying sister axes apparently lie one above the other, with the chromatin from both sisters extending outward from the conjoined axis. This linear loop array is likely a modified version of a corresponding intermediate found in mitotic chromosomes at early prophase (see 117). Each sister pair begins to develop a shared kinetochore during this period.

In organisms that do not exhibit premeiotic pairing, homologues probably begin to interact during early leptotene, though earlier interactions are not excluded. The pairing process appears to involve physical interactions between chemically intact homologues at many positions. Homologue pairing in early meiosis may be closely related to that which occurs in nonmeiotic cells.

Initiation of recombination appears to be functionally distinct from (and usually subsequent to) some degree of homologue pairing, although pairing and recombination could comprise a more-or-less continuous series of events that occur at the same or related positions. In yeast, most or all recombination is initiated via double-strand breaks (DSBs); DSBs are converted to double Holliday junctions and, thence, to recombination products (Figure 4). The same basic events probably occur in all organisms. Meiotic recombination appears to be an adapted and enhanced version of recombinational repair processes in nonmeiotic cells.

The total number of recombinational interactions along a chromosome is likely large, particularly for organisms with long chromosomes, with a small subset of such interactions finally developing into crossovers. The number and distribution of crossovers along and among chromosomes is tightly controlled such that, along each bivalent, crossovers are minimal in number (i.e. at least one) and, if more than one is present, maximally spaced.

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Figure 3 Stages of meiosis in *Saccharomyces cerevisiae* as defined by fluorescence microscopy of squashed, DAPI-stained nuclei. (*a*) Premeiotic G1; (*b*) bulk S-phase; (*c*) late S-phase with concomitant loss of nuclear cohesiveness; (*d*) preleptotene chromosome compaction; (*e–g*) leptotene; (*h*) early zygotene; (*i*) mid-zygotene synizetic knot; (*j*) late zygotene bouquet; (*k*) pachytene; (*l*) late pachytene/diplotene, onset of diffuse stage (and moth-eaten synaptonemal complex). Note lower intensity diffuse plus punctuate features correspond to mitochondrial DNA. Bar = 10μ [from Padmore (222)], correlated directly with other processes (223).

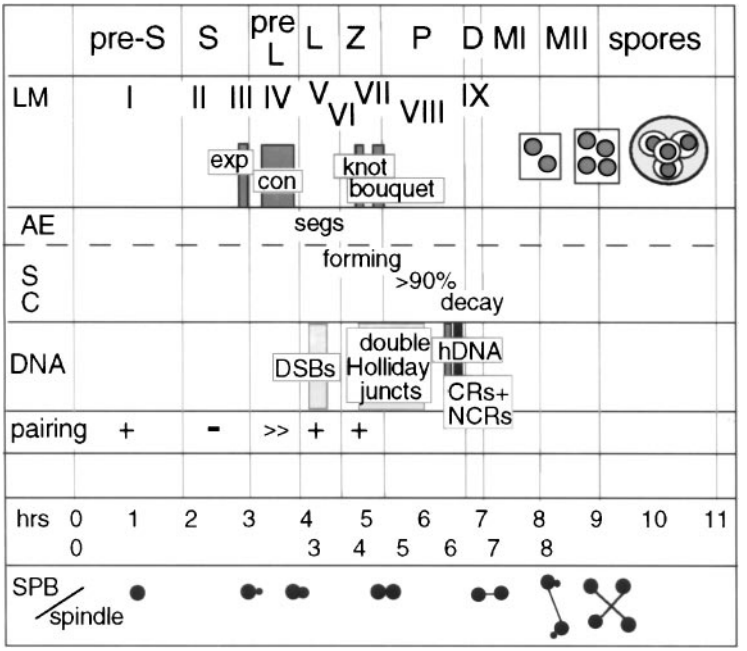


Figure 4 Events of meiosis in *Saccharomyces cerevisiae*. LM (light microscopy) stages from Padmore (222) (see Figure 3). AE, Axial elements; SC, synaptonemal complex; and SPB, spindle pole bodies (from References 223, 222, 3, respectively). MI, Metaphase I; MII, metaphase II; DSB, double-strand breaks; CRs, crossovers; NCRs, noncrossovers. DNA analysis from References 223, 254, 272.

Concomitant with intermediate and late stages of recombination, the axial elements of paired homologues become closely juxtaposed along their lengths via additional proteins, with resultant formation of the tripartite synaptonemal complex, SC, a prominent and universal feature of meiosis the precise role of which is not established. The SC might be required for promoting certain steps of recombination, stabilizing recombinational interactions, mediating crossover interference, maintaining the axis-association of crossovers, or keeping homologues connected after the point at which the only interstitial connection between them is one or a few crossovers (Figure 4) (160, 245).

At the late-leptotene through pachytene stages, two types of nodular structures are observed in association with the chromosome axes: early nodules, which likely correspond to DSBs and/or prior pairing interactions, and late nodules, which correspond to the subset of recombinational interactions that will or have become crossovers (52). Early nodules first occur between paired

homologue axes prior to SC formation and then, sometimes, atop the SC, while late nodules sit inside or atop the central region of the SC (e.g. 7, 52, 262).

Late prophase and beyond Pachytene is followed by diplotene (Greek "diploos" = double). Transitional stages include a diffuse chromatin condition (see Figure 3*l*) (131b) and progressive loss of SC components and nodules after which chromosomes again individualize. In the classical diplotene configuration (Figure 2*e*), homologues are widely separated (in repulsion) but remain held together at the chiasmata (Greek "chiasma", plural "chiasmata" = beams arranged in a cross in the framework of a roof), and eventually, sisters become more distinct. In organisms with favorable cytology (e.g. grasshoppers) (see 149), the four strands of each bivalent are visible. Cytological and BrdU labeling studies make it clear that sister chromatids are coaligned along their lengths and that chiasmata are sites at which two non-sister chromatids of two homologues are connected to one another, either in an open cross or an overlapping configuration (152, 153). The final stages of prophase are diakinesis (Greek, "kinesis" = movement) and prometaphase (Figure 2*f–h*). During these stages, bivalents continue to shorten and compact until, by metaphase I, they are nearly as short as their mitotic metaphase counterparts. Sister chromatids continue to act as a single structural unit throughout this period, as illustrated dramatically by the coordinate coiling of sister axes as a pair of parallel structures at diakinesis in lily (270).

The events of the two meiotic divisions then ensue (Figure 2*i–o*), kinetochores having developed throughout prophase and prometaphase and continuing to undergo morphogenetic changes during the two division cycles. The kinetochore of each homologue is often morphologically unitary, or effectively so, through prometaphase I, to promote coordinate attachment of sister chromatids to the same pole (213).

Scope and Rationale of this Review

A complete review of meiotic chromosome metabolism would include many aspects, including S-phase, the SC, all aspects of meiotic recombination, and the interrelationships of these processes with each other and with the cell cycle. Limitation in space led us to focus first on one of the key points in the transition from a mitotic to a meiotic prophase program and, thus, to illustrate one of the most fascinating aspects of reviewing meiosis: the difficulty of unraveling the tangled skein of interrelations between the different actors of the show.

While the program of meiotic chromosome metabolism is complex at all stages, particularly during prophase, the leptotene/zygotene transition appears to be a point at which many diverse cellular influences come to bear in an unusually complex and critical transition.

One universal hallmark of this transition is the formation of the chromosomal bouquet, which is the midpoint of a dynamic change in the status of chromosome ends and a constellation of overall changes in nuclear and cellular organization. The bouquet stage is transient and also is fixed in timing with respect to other events of chromosome metabolism. This suggests that the meiotic program is driven forward by cell cycle regulatory transitions and provides a convenient point of reference.

The bouquet stage also represents a transition point in the recognition and juxtaposition of homologues: "pairing" in the most general sense. The available evidence suggests that the three types of interhomologue interactions (see above) often, perhaps always, occur in a semi-overlapping "bucket brigade," in approximate temporal succession, and with each type of interaction partially but not absolutely dependent on the other, with each interaction simplifying the job for the next. The bouquet stage lies exactly at a transition point among all these interactions.

The leptotene-zygotene transition is critical in other aspects. Active, as well as passive, chromosome movements occur at this stage, at least in some organisms. The recombination process undergoes several critical transitions in and around this period, including axis-association, progression through two early steps, and, perhaps, the decision as to which recombinational interactions will be resolved as crossovers. Finally, at about the time of this transition, chromosomes seem to undergo a series of cyclic genome-wide changes in overall chromatin/chromosome structure. These component processes and their interrelationships are discussed.

THE BOUQUET STAGE

A Universal Feature of Meiosis

In midmeiotic prophase, telomeres occur in a polarized organization, called the bouquet: All chromosome ends are directly attached to the inner surface of the nuclear envelope and are grouped together within a limited area (Figures 5, 6, and 7). This stage is so obvious in most meioses that it was first described in the early 1900s (96; for reviews, see 58, 73, 81, 108, 133, 176, 242, 250).

The bouquet stage occurs universally at the leptotene/zygotene transition, apparently transiently (see below). The bouquet stage is essentially contemporaneous with the onset of SC formation (Figure 7). In yeast, it is concomitant with the progression between DSBs and stable strand-exchange intermediates (double Holliday junctions) (47a, 89, 222, 254; H Scherthan, personal communication) (Figure 4). In organisms with definite centrosomes, e.g. animals (199) and fungi (53), the region of the nuclear envelope containing the colocalized telomeres generally faces the centrosome and polarization is tight. However,

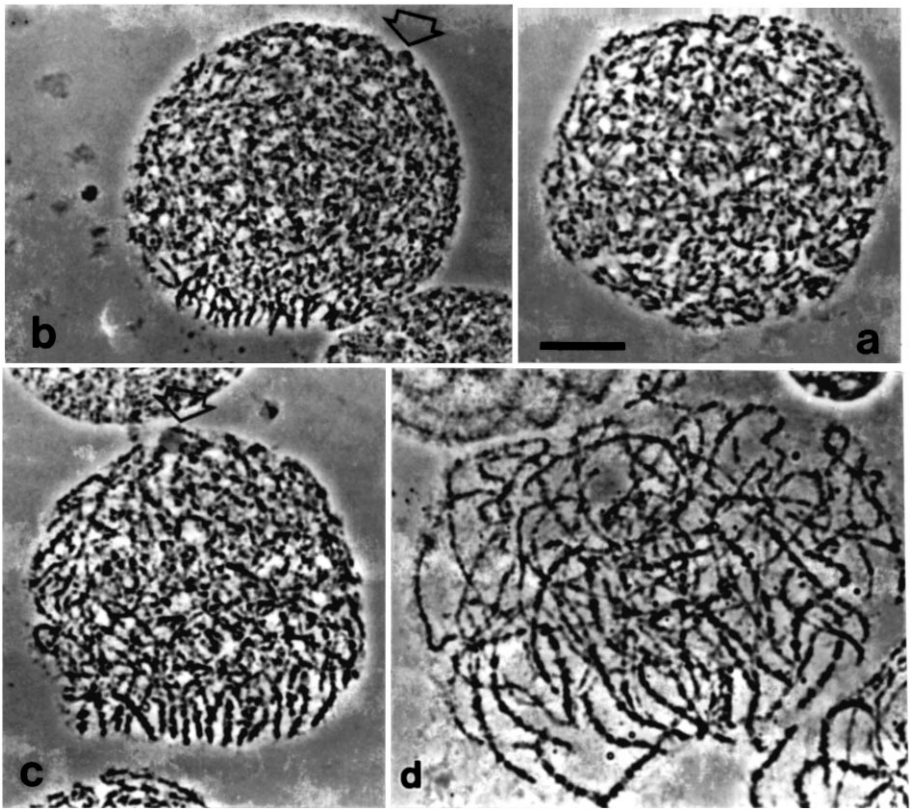


Figure 5 Beautiful illustration of bouquet formation in the crowded nucleus of salamander. (*a–d*) Note also the increase in the nuclear volume (From 156).

bouquet formation is also observed in plants, which lack distinctly localized microtubule organizing centers; there the area of clustering is broader (114, 176, 282). Thus, bouquet clustering is not due to specific interaction of the chromosome ends with the centrosome. In several organisms, zygotene chromosomes are clumped in a dense tangle, the synizetic knot, suggested to be equivalent to the bouquet (149). In budding yeast, however, a synizetic knot and a bouquet are both observed, in successive zygotene stages (222) (Figure 3*i*,*j*). The two morphologies apparently differ only in the degree of chromatin compactness.

Absence of a bouquet arrangement has been reported for a handful of organisms, but most such conclusions are likely not true. In some cases, such a report was corrected after investigation with a different method (for *Lilium*, compare 139 and 139). In other cases, the failure to observe such a stage could be due to

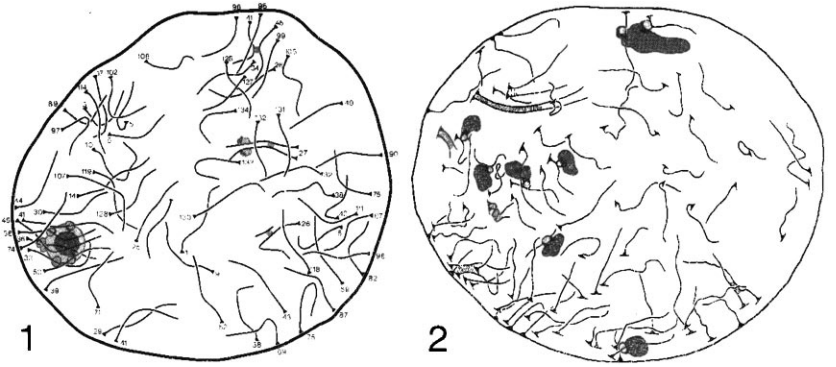
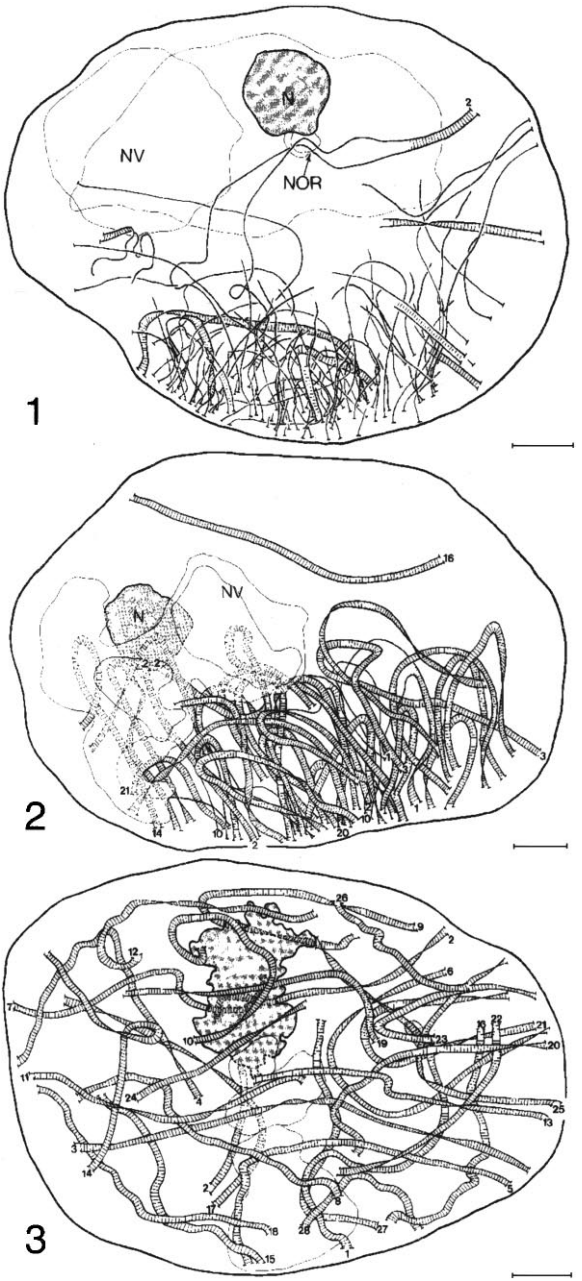


Figure 6 Three-dimensional reconstruction of two leptotene nuclei from human oocyte (*1*) and spermatocyte (*2*): All telomeres are attached to the nuclear envelope. (*1*) No bouquet is formed but some telomeres are partially grouped. (*2*) Synaptonemal complexes are initiated in five homologues although there is only weak polarization of part of the chromosomes. (From 36, 240.)

the fact that visualization of chromosomes within zygotene nuclei can be difficult because of the synizetic knot (81; see also below). Also, although occasionally bouquet formation can be followed on unstained cells in favorable material (see 156) (Figure 5), it is usually difficult to investigate the spatial distribution of the chromosomes at early prophase stages by light or electron microscopy, especially in organisms with chromosomes the lengths of which span the nuclear diameter several times (e.g. 146). Similarly, some electron microscope studies are not conclusive owing to the small sample of nuclei investigated. And finally, in some species, the bouquet formation may be very transient (see 253).

Nonetheless, a few organisms do seem to exhibit a variant situation. In several nematodes, including *Caenorhabditis elegans*, only one end of each chromosome becomes attached to the nuclear envelope, and these ends do not cluster (120, 121, 123–126). However, every end may have the potential to attach (122, 126). A Rabl orientation is maintained during meiotic prophase in spermatocytes of the mosquito *Aedes aegypti*. Homologues are somatically tightly paired, and during meiotic prophase, their centromeres remain clustered and attached to the nuclear envelope whereas the telomeres, initially attached to the nuclear envelope, become more or less associated but free in

Figure 7 Bouquet formation and release in *Bombyx* oocytes. (*1*) Mid-zygotene nucleus; (*2*) late zygotene; (*3*) pachytene, release of the telomere clustering. NV, nuclear vacuole; N, nucleolus; NOR, nucleolar organizer. (From 238.)



the nucleoplasm. However, neither the centromeres nor the telomeres face the centrioles (296). There is also little evidence of a bouquet stage in *Drosophila melanogaster*; instead, physical clustering of heterochromatic centromeric regions and weak polarization of telomeres to the opposite half of the nucleus is observed (50; A Carpenter, personal communication), seemingly more reminiscent of a Rabl orientation than a bouquet. Since *Drosophila* telomeres are comprised of transposable element sequences and lack the usual telomeric repeat sequences (e.g. 227), this organism could be atypical. On the other hand, in all these organisms, axial elements (AEs) appear concomitant with SC formation; thus, a true bouquet stage might have existed earlier but be lost by the time SCs are visible.

The Bouquet Is Not a Simple Reinforcement of the Rabl Orientation

In nonmeiotic cells of a large variety of organisms, chromosomes exist in the so-called Rabl configuration: Centromeres are clustered at one pole of the nucleus while telomeres are left hanging in the other half. This configuration develops as a consequence of the anaphase movement of the centromeres toward the spindle poles and persists during the subsequent interphase (236; see references in 15, 62, 66, 67, 81, 108, 129, 132, 134, 250). The bouquet is often said to be a relic of the Rabl chromosome orientation created during the last premeiotic mitosis (58, 73, 108, 149, 207, 282). This is not exactly true, however.

First, while chromosomes are polarized in both the bouquet and Rabl configurations, chromosomes in the bouquet no longer have their centromeres but instead their telomeres, facing the centrosome (e.g. 53, 199). Thus, bouquet formation requires that (*a*) centromeres separate while telomeres cluster and (*b*) the chromosomes switch their orientation with respect to the centrosome.

In addition, in the bouquet, all chromosome ends, irrespective of arm length, are directly attached to the inner membrane of the nuclear envelope often via special attachment plaques (see below) and are strongly polarized; the chromosomes, thus, loop out from their attachment regions (Figure 7). In the Rabl configuration, in contrast, the telomeres seem often to be "hanging" from the centromeres (see 107). Also, some chromosome ends may be associated with the nuclear periphery in the Rabl but others may tend to lie internally (e.g. 25, 162, 192, 253), and no differentiated telomeric attachment structure has been reported in a nonmeiotic cell type. Also, in somatic cells, telomeres may be either more or less clustered (e.g. 25, 107, 162), presumably because of variability in arm lengths (241). In extreme cases, telomeres form chain-like end-to-end associations (14, 71). Thus, in somatic cells, telomere disposition arises more or less passively, as a consequence of other determinants of chromosome organization (e.g. 135, 136, 192, 193, 221), whereas in meiotic prophase,

the telomeres arrive in the bouquet configuration via a more actively directed process.

The difference in centromere clustering that occurs during the change from the Rabl orientation to the bouquet is exemplified by *Allium fistulosum* (59). Both root-tip interphase and premeiotic interphase nuclei exhibit a clear polar cluster of mainly nonhomologous centromeres (not attached to the nuclear envelope) with telomere-associated heterochromatic ends at the opposite pole. In zygotene, in contrast, centromeres are no longer clustered but instead are distributed throughout the nucleus, often separated by great distances. The same progression has been documented by other serial sectioning studies (reviewed in 293) and by 3D FISH (11, 253). In fact, the difference in telomere configuration between the two situations explains why centromere clustering must be lost during the bouquet stage: In the Rabl, with centromeres clustered, the ends of shorter arms are at a different "latitude" than the ends of longer arms; in the bouquet, in contrast, with all chromosome ends at the same position and chromosomes bent over in the middle, centromeres of different chromosomes must occur at different positions according to the differing ratios of chromosome arm lengths (e.g. 110).

Second, the bouquet is a special feature of meiosis. In most nonmeiotic cells, a Rabl orientation is preserved through the cell cycle. An elegant study of mitotically dividing *Allium cepa* root tip nuclei reveals conservation of the Rabl throughout G1, S, and G2 (107, 108). The same it true for Indian muntjac, (269), *Drosophila* (134, 192, 193 and references therein), *Saccharomyces cerevisiae* (128, 148), and *Schizosaccharomyces pombe* (104). Thus, loss of the Rabl orientation during meiosis must be especially programmed. Accordingly, centromere clustering is lost abruptly during early meiosis in mammals (253) and yeast (148).

In addition, 3D analyses often detect no Rabl configuration in nonmeiotic cells, e.g. several cell types of mouse and human (166, 184, 190, 294); a clear bouquet is, nevertheless, formed during meiosis in these cases (240, 253). Also, weak telomere polarization sometimes occurs in non–germ line cells but varies among species and among different tissues of the same organism (75). Such clustering is always modest compared with that seen during meiosis (57, 81, 108). Also, in yeast, somatic telomere clusters occur but strong spindle pole body (SPB)-oriented centromere clustering is still present (e.g. 127, 128, 148, 162).

The Bouquet Is a Transient Intermediate in a Dynamic Program of Chromosome End Reorganization

Ultrastructural analysis has revealed that telomeres are free of nuclear envelope attachments at early leptotene. Telomeres first become anchored all around the

inner surface of the nuclear envelope at mid to late leptotene, with no or weak polarization (Figure 6), and then migrate into a bouquet configuration at late leptotene (e.g. 36, 240, 311). The bouquet configuration disappears at pachytene via progressive dispersal of telomeres around the inner periphery of the nuclear envelope (Figure 7) (222, 238, 240). The full bouquet likely represents a relatively short, specific transitional stage, as bouquet-stage nuclei comprise a small fraction of all prophases (222, 250, 253; D Zickler, unpublished data; H Scherthan, personal communication). In some organisms, e.g. grasshoppers *Locusta migratoria* and *Keyacris scurra*, the centrosomes probably play a role in the pachytene dispersal because some of the clustered SC ends follow one pair of centrioles as they migrate (100, 200). But in most organisms, the centrosome (and SPB) separation occurs after the release of the telomeres from the bouquet (reviewed in 250, 293). Finally, chromosome ends detach from the nuclear envelope during the latter part of pachytene and/or the transition from pachytene to diplotene (e.g. 222, 240).

An interesting variation on the normal theme occurs in the achiasmatic triploid females of *Bombyx mori* and in triploid rainbow trout spermatocytes. Although the three homologues are coaligned at zygotene, only two are synapsed by SCs; the third lies parallel. At pachytene, only the two homologues synapsed by an SC get dispersed on the nuclear periphery. Most leftover univalents remain in a bouquet configuration and start a second round of SC formation, this time along themselves or between nonhomologous chromosomes. Only at the very end of pachytene do the nonhomologously synapsed chromosome ends become evenly distributed around the periphery and then, in turn, detach (219, 239).

Envelope association and bouquet formation are, thus, two functionally distinct aspects of telomere behavior. Association is present before and after, as well as during, the bouquet stage. Telomere migration around the envelope, into and then out of the bouquet, is a second process, superimposed upon the first.

No analogous program of changes occurs during mitotic prophase (59, 294). Also, the bouquet is structurally distinct from the general "clustering of heterochromatic regions" often observed in nonmeiotic cells (81). Instead, bouquet formation involves directed, polarized movement of inner-membrane–attached chromosome ends around the nuclear envelope inner surface.

How Does the Bouquet Arise?

The Rabl orientation is substantially disrupted during premeiotic interphase and early prophase (25, 148, 253) whereas the mature bouquet configuration is seen at the leptotene/zygotene transition (see above) (reviewed in 58, 81, 108, 176, 250, 293).

Bouquet formation involves a progressive series of spatial changes, as inferred from EM serial reconstructions. First, at early stages only some of the telomeres are attached to the nuclear envelope, and no polarization is seen (e.g. 36, 240, 311). Ends are attached to the nuclear envelope prior to the bouquet regardless of whether axial elements are made in prophase relatively early (Figure 6) or relatively late (e.g. 56). Second, mid-leptotene nuclei show various degrees of telomere subgrouping but still without any obvious bouquet (Figure 6) (e.g. 36, 240). In *Sordaria*, smaller chromosome ends are clustered, whereas in the same nucleus, larger chromosomes have only one pair of aligned telomeres in the bouquet region, and the two others are still attached in opposite regions of the nuclear envelope (311). Similarly, clustering of the nucleolar organizing homologues is sometimes delayed relative to the rest of the chromosomes (e.g. 57).

The timing and pattern of bouquet emergence is extensively documented in human spermatocytes (240, 253). The first stretches of AEs are mainly telomeric; these ends are seen already attached to the nuclear envelope but still distributed over most of its surface (Figure 6). Even the first stretches of SC form when telomeres are only slightly polarized (240) (Figure 6). Peripheral association of telomeres prior to bouquet polarization is also seen by FISH analysis in human as well as in mouse meiosis (253). In the latter cases, telomeres move toward the centrosome area during most of leptotene and even early zygotene; centromeres, in contrast, remain pressed to the nuclear periphery at early leptotene but are found in the nuclear interior when the bouquet is formed. Interestingly, Golgi clustering around the centrosome, a characteristic feature of the bouquet stage, is already present when AEs appear at early leptotene (for humans, see 240; for *Bombyx*, see 238), which implies that some asymmetry in the nucleus precedes polarization of the chromosomes and other nuclear envelope components (see below). In maize, telomere clustering in the bouquet (113, 203; reviewed in 114) is shown by FISH analysis of optically sectioned nuclei (25) (Figure 8) to occur at the leptotene/zygotene transition, identified in this case by specific chromatin changes (74). Coincidently, the nucleolar region relocates from the center of the nucleus toward the bouquet (25, 282). Because nuclei of intermediate stages were rarely observed, telomere attachment to the nuclear periphery was proposed as occurring directly in a polarized configuration, without prior peripheral association (25). This interpretation contrasts, however, with the universal observation of intermediate stages in ultrastructural analyses of leptotene nuclei (Figures 6, 7) (reviewed in 293). More probably, intermediate stages occur, but transiently. In budding yeast, centromeres undergo an abrupt transition from the clustered (Rabl) to a nonclustered configuration during early meiotic prophase (148). Maybe loss of centromere clustering is

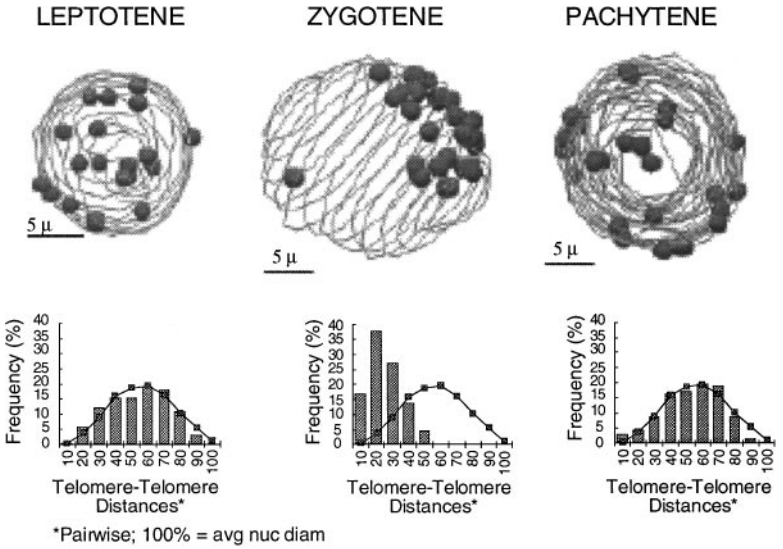


Figure 8 Changes of telomere position during meiosis in *Zea mays* as analyzed by three-dimensional fluorescence in situ hybridization (25). Distances between all pairs of telomere signals (each with *x*, *y*, and *z* coordinates) have been normalized to the nuclear diameter and plotted as frequency histograms (*bar graphs*). For comparison, the distribution of distance pairs for random points in a sphere is included (*line graphs*). Actual models from the three-dimensional stacks are included to show the edge of the nucleus (*wire frame*) in relation to the telomere signals (*balls*). Scale bar is 5 μm). (Courtesy HW Bass, WZ Cande, and JW Sedat; see Reference 25.)

related to either a late S-phase loss of nuclear cohesivness or to the ensuing preleptotene compaction stage (Figure 3*d*).

A unique program occurs in *S. pombe*. In zygotic meiosis, a bouquet configuration arises prior to the onset of meiosis and persists throughout meiotic prophase. Time-lapse microphotography of living cells, with parallel analysis of centromeres, telomeres, and the SPB (53) showed that the switch of telomere position relative to the SPB occurs in the G1 phase preceding karyogamy and premeiotic DNA replication: In vegetative cells and after meiotic anaphase I, centromeres are clustered near the SPBs in a typical Rabl orientation (see also 104), but from karyogamy to the end of meiotic prophase I, telomeres were found facing the SPB (53; reviewed in 163). The same contrast occurs in azygotic *S. pombe* meiosis (251). Centromere release from the SPB may depend on events that occur during conjugation because, in haploid cells induced to the sexual cycle, initially, centromeres and telomeres are both clustered near the SPB (54).

Other fungi do not exhibit this same behavior. In *S. cerevisiae* karyogamy, centromeres are clustered at the SPB site of the nuclear envelope, and the two

sets of chromosomes are joined in a typical Rabl orientation before entering meiosis (46, 47) and, thence, a normal bouquet. The same scenario is probably also true for Basidiomycetes such as *Coprinus lagopus* (181, 183). In the filamentous ascomycetes *Neurospora crassa* and *Sordaria macrospora*, the two haploid nuclei of the dikaryotic cell show a clear Rabl organization (284), but after nuclear fusion, the two haploid sets of chromosomes first lie separated in the zygote nucleus, each with its respective SPB (195, 237, 264, 284). Homologues are brought into a joint domain at the time of nucleolar fusion, and EM analyses show that at early leptotene, telomeres are anchored all around the nuclear envelope, with only one chromosome end attached to the SPB site. This single chromosome (or bivalent) attachment to the SPB persists even during the clustering of the telomeres into a bouquet, but different ends and bivalents can be SPB-attached (37, 39, 311; D Zickler, unpublished data).

Bouquet Formation Does Not Require Interactions Between Homologues

Bouquet formation has been seen in several haploid meioses (for rye, see 76, 249; for trihaploid wheat, see 297) and in the asynaptic *as1* and *asb* tomato mutants (131). Also, in the *rec8-110* mutant of *S. pombe*, in situ hybridization shows impaired interstitial and centromeric pairing whereas telomere clustering remains unaffected (204). Thus, the bouquet results from a specific program of changes in 3D chromosome disposition (in coordination with other cellular and nuclear changes; see below) and is not an indirect byproduct of homologous chromosome pairing or synapsis.

The Bouquet Is Part of a General Nuclear and Cellular Reorganization

Polarization of telomeres is accompanied by other important changes in both nucleus and cytoplasm. First, the nucleus enlarges between early leptotene and pachytene (e.g. 82, 140, 156, 168) (Figure 5). Second, the nucleolus relocates from the center of the nucleus to the area where the bouquet is forming [e.g. lily nucleoli are clustered with the centromeres before fusion (58, 59, 139) in Sordaria (311), rye and wheat (282), Tradescantia (130), and maize (25)]. In rye and wheat, where nucleolar organizers (NORs) are close to short-arm telomeres, the process of nucleolar fusion and movement was proposed to arise from telomere clustering, as both processes are sensitive to colchicine (282; see also 33). However, the nucleolus is a most prominent and important nuclear structure, and therefore it seems possible that nucleolar repositioning might occur via a more directed process. Indeed, in maize and grasshoppers, nucleolar movement appears to occur after colocalization of most telomeres into the bouquet, in the latter part of the bouquet stage (25, 57). Perhaps there is an intrinsic

affinity between the NOR and the bouquet area of the nuclear periphery, with chromosome repositioning via bouquet helping indirectly, e.g. by promoting movement or by moving the bulk of the chromosome mass into a more confined area, leaving more freedom for nucleolar migration. Third, the shape and structure of the nuclear membrane change at about the time of the bouquet (see below). When strong invaginations are seen during premeiotic interphase, these are eliminated during meiotic prophase (57, 238). Fourth, the polarized chromosomal arrangement often parallels a polar distribution of cytoplasmic organelles, with mitochondria and Golgi aggregates facing the telomere cluster (e.g. 36, 57, 199, 238). Both polarities disappear at late pachytene, when the centrioles move toward the opposite poles at the same time as the telomeres get more evenly distributed on the nuclear membrane (238). Finally, in some organisms, nuclei are seen relocated eccentric and close to the cell membrane or facing the cytoplasmic channels (fusosomes) connecting the meiocytes (133, 238).

The Bouquet Is Part of a General Reorganization of Nuclear Envelope Contents

STRUCTURALLY DIFFERENTIATED ANCHORING OF CHROMOSOME ENDS TO THE INNER NUCLEAR MEMBRANE In nonmeiotic cells, even in cases where distal regions of chromosomes are associated with the nuclear periphery, no morphologically obvious connection between chromosome ends and the nuclear envelope has been reported (e.g. 77, 184). In meiotic chromosomes, in contrast, ultrastructural analysis reveals a direct continuity between the ends of each AE and the inner membrane of the nuclear envelope, with a differentiated attachment plaque (a dense plate-like or cone-shaped fibrillar structure) in most organisms studied (36, 56, 83, 90, 97, 130, 139, 179, 199, 208, 239, 240, 268). Even when chromosomes are telocentric, the kinetochore ends are seen attached to the nuclear envelope via thickened attachment plaques (303). This terminal differentiation arises on the chromosome ends prior to their attachment to the nuclear membrane (e.g. 238). Interestingly, in human oocytes and spermatocytes, the telomere attachment sites are connected by a bundle of microfilaments to 100- to 150-nm spherical dense bodies located on the cytoplasmic side of the nuclear envelope, seen only at zygotene and early pachytene when the bouquet is present (36). Existence of a tight connection is also illustrated by the maintenance of the bouquet in spreads (e.g. for yeast, see 89, 222) and the presence of filaments linking telomeres of budding yeast to nuclear pore clusters (see 162). Because attachment of chromosome ends precedes SC formation (e.g. 199), telomeric attachment is an intrinsic property of each homologue rather than of the synapsed bivalent.

In situ hybridization analysis of pachytene chromosomes in mice shows that the telomeric repeat sequences (TTAGGG)n are tightly localized to the

structural axes rather than to the chromatin loops surrounding the ends (202). Possibly the specialized integration of telomeric repeat sequences into the axes is an integral part of the membrane attachment structure.

Protein components of the terminal plaque structure are not known. Candidates in budding and fission yeasts could be the recently described meiosis-specific proteins Ndj1/Tam1 and Taz1 that exhibit strong preferential telomere localization independent of chromosome pairing and synapsis (55, 63, 64; see also section below). Absence of the Ndj1/Tam1 protein results in grossly aberrant telomere organization, as evidenced by reduced incorporation of the telomere-binding protein RAP1 and defective association between homologous telomeres (63). In vegetative budding yeast cells, Sir3 and Sir4 proteins are required for the telomeric localization at the nuclear periphery but not for clustering (60, 84, 127, 224); also, Ku protein is required for normal telomere organization (170).

Finally, a prominent component of the inner surface of the nuclear envelope is the lamins. Meiosis-specific differentiation of lamins is known (165). In mammalian primary spermatocytes, the nuclear lamina is composed of two germ line–specific lamina proteins together with lamin B whereas the mitotic lamins A/C and B2 are not detected (9, 106, 265, 289).

ACCOMPANYING POLARIZATION OF NUCLEAR PORES In the bouquet configuration, clustered telomeres are strikingly located close to areas of aggregated nuclear pores whereas the rest of the nucleus is almost devoid of both pores and telomeres; however, the immediate telomere attachment area per se is devoid of pores (56, 113, 139, 203, 268; WZ Cande, personal communication) (Figure 9). Location of these components near the centrosome, or as in higher plants when centrosomes are absent, toward the bouquet area, could also include specific interactions between the pores and the cytoplasmic cytoskeleton, possibly in relation to microtubule-dependent chromosome movements (see below). Pore polarization clearly occurs de novo during meiotic prophase: Pores of premeiotic interphase cells are distributed throughout the envelope (see 56, 57; see also 167; WZ Cande, personal communication). Apparently bouquet formation is part of an overall polarization of nuclear envelope contents in which all integrally associated components, including both attached telomeres and pores, move toward the centrosome/microtubule organization center (MTOC)/SPB region (or vice versa), with inter-telomeric associations tending to exclude the pores.

MECHANISM OF FORMATION AND RELEASE Polarization of chromosome ends into the bouquet could be accomplished by diffusion of nuclear envelope components directed by an attracting or repelling gradient, e.g. directed by

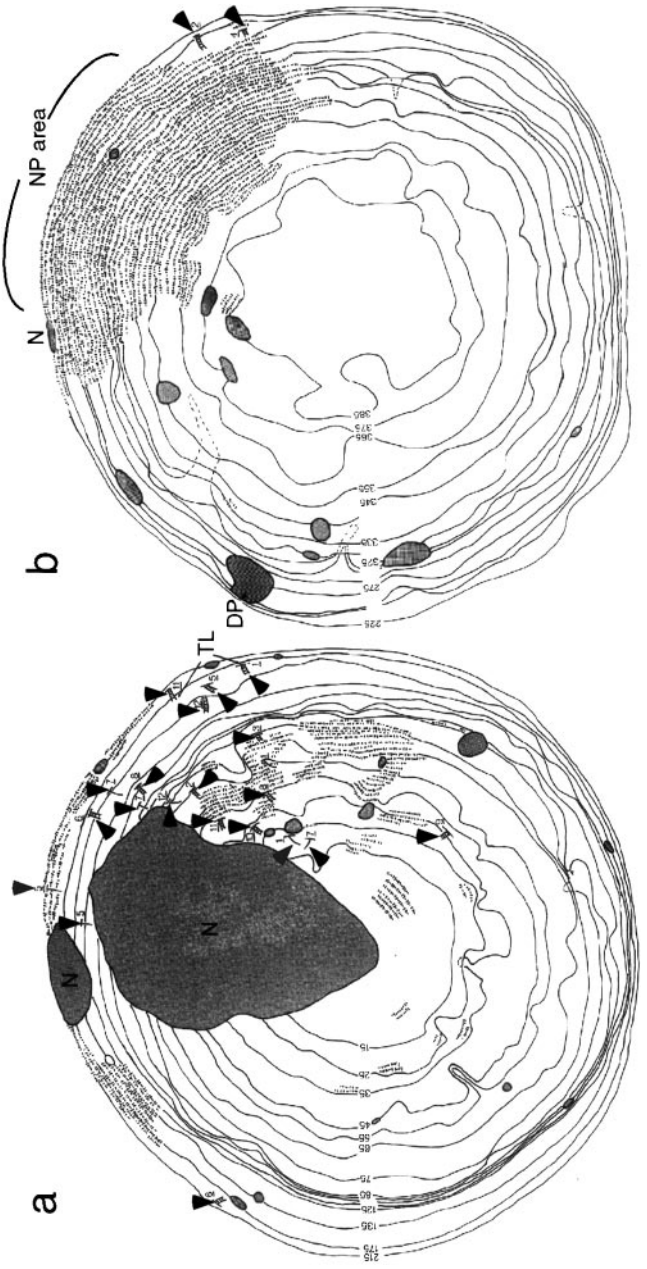


Figure 9 Three-dimensional reconstruction of a mid-zygotene nucleus of lily at the bouquet stage, two halves of the same nucleus. All telomeres (TL) (marked by *triangles*) are grouped on the left half (*a*), whereas all nuclear pores (*small ticks*) are seen in the right half (*b*). (*Dark areas*) represent nucleoli. (From Reference 138.)

the centrosome/SPB. Alternatively, motor proteins and/or microtubules are sometimes proposed to be involved. For example, in plants, where the entire nuclear envelope is an MTOC, envelope-associated cytoplasmic microtubules (MT) (259) or, analogously in mammals and fungi, astral microtubules (176) could be involved. Cortical cytoplasmic microtubules are, however, not involved: Their removal by treatment with microtubule inhibitors does not inhibit bouquet formation in rat (248) or maize (WZ Cande, personal communication). The bouquet configuration and pore clustering are released together in midpachytene (176, 248, 259). This change is not accomplished by simple stiffening of the pachytene chromosomes because such a process would not suffice in organisms with long chromosomes. Thus, changes in nuclear envelope organization, e.g. release of polarization constraints, seem more likely. In cases where unsynapsed bivalents remain behind after synapsed chromosomes exit the bouquet, however, chromosome configuration clearly plays a role.

Related Processes Occur in Nonmeiotic Cells

NUCLEAR PORE BEHAVIOR Clustering of nuclear pores is observed as a prevalent phenotype of certain nucleoporin mutants, in stationary yeast cultures, and during apoptosis (28, 88). However, opposite to what is observed in a bouquet, the clustering of the nuclear pores in a *nup113* mutant is independent of the subnuclear distribution of the telomeres: The Rap1 foci groupings are identical to those in wild-type nuclei (127).

The nucleoporin mutants that exhibit this phenotype are, thus far, specifically those defective for mRNA export. If this is a direct effect, it might provide a hook for identification of other components involved in nuclear envelope organization. Alternatively, the change in pore distribution could be an indirect consequence of altered mRNA trafficking rather than of an alteration in the nature of the pore per se. Regardless, the occurrence of a bouquet as a mutant phenotype argues against the simple idea that random disposition is the default and that the meiotic bouquet is created de novo (e.g. via a motor-driven process). Instead, bouquet formation might result from the transient disruption or inhibition of some housekeeping function of nonmeiotic cells rather than by positive creation of an entirely new, specifically designed process. More generally, the fact that polarization occurs as a mutant phenotype suggests that the unpolarized configuration must be actively promoted. Perhaps a single positive force is involved that would then be lost to give the meiotic bouquet. More likely, the promoting force would be one partner in a homeostatic pair of opposing forces whose exact balance determines the final outcome, differently in different situations.

In addition, GFP tagging of a nucleoporin protein (Nup49p) demonstrated that, during conjugation, the nuclear pore complex can move over the nuclear surface and that clusters form by the movement of preexisting nuclear pore complexes, providing a second example in which clusters of nuclear pores form

by migratory movement of preexisting nuclear pore complexes (45). Finally, 3D reconstitution of budding yeast nuclei showed that whatever the moment in the cell cycle, pores are never completely evenly distributed over the nuclear envelope, e.g. SPBs are found in or adjacent to a region of highest nuclear pore density (302). Thus, in yeast, the nonmeiotic cell type apparently exhibits a tendency toward the same condition that occurs in strongly pronounced form and universally at the meiotic bouquet stage.

CHANGE IN CHROMOSOME ORIENTATION RELATIVE TO CELLULAR ORIENTATION Nuclear rotations are seen in nonmeiotic cells. In *Pisum sativum* and *Vicia Faba*, the nuclei of sister root cells (i.e. two cells resulting from a single mitotic division) exhibit a clear Rabl configuration; after mitosis, however, instead of the two chromosome groups opposing one another, as expected from maintenance of the telophase arrangement into interphase, the two groups lie side by side, each with the same orientation perpendicular to the axis of the preceding division (241). Thus, either the nucleus or the telomeres within the nucleus rotate relative to the overall orientation of cells within the tissue.

Possible Functions of the Bouquet

Being dramatic in nature, unique to meiosis, and highly conserved, the bouquet conformation itself, or perhaps the act of forming or dissolving the bouquet, must play an important role for meiotic cells. We assume that the bouquet is important for its effects on the chromosomes rather than occurring for some other reason and affecting the chromosomes accidentally as a consequence of the strong attachment to the nuclear envelope. The bouquet is often proposed to play a role in homologue pairing. It seems unlikely that bouquet formation promotes the first specific contacts between homologous chromosomes, but the idea of significant role(s) in intermediate stages of homologue juxtaposition is (are) attractive. The bouquet might also provide a backup mechanism for bringing together homologue pairs that failed to colocalize at the normal time. Alternatively, or in addition, the bouquet could be important for overall nuclear organization irrespective of homologue pairing, to reestablish an orderly arrangement after loss of the Rabl and the disruptive events of chromosome pairing, or to place particular regions, the nucleolar organizer, or others within appropriate spatial domains, as required for optimal gene expression and trafficking between nucleus and cytoplasm. A mature bouquet configuration might be required only indirectly, to permit active, telomere-directed chromosome movement; also, telomeres and their attachment to the nuclear envelope may be important irrespective of the bouquet (see below).

AN IMPORTANT CONSTRAINT Movement of telomeres into the bouquet will affect a length of adjacent chromosome that is of the same order as the diameter

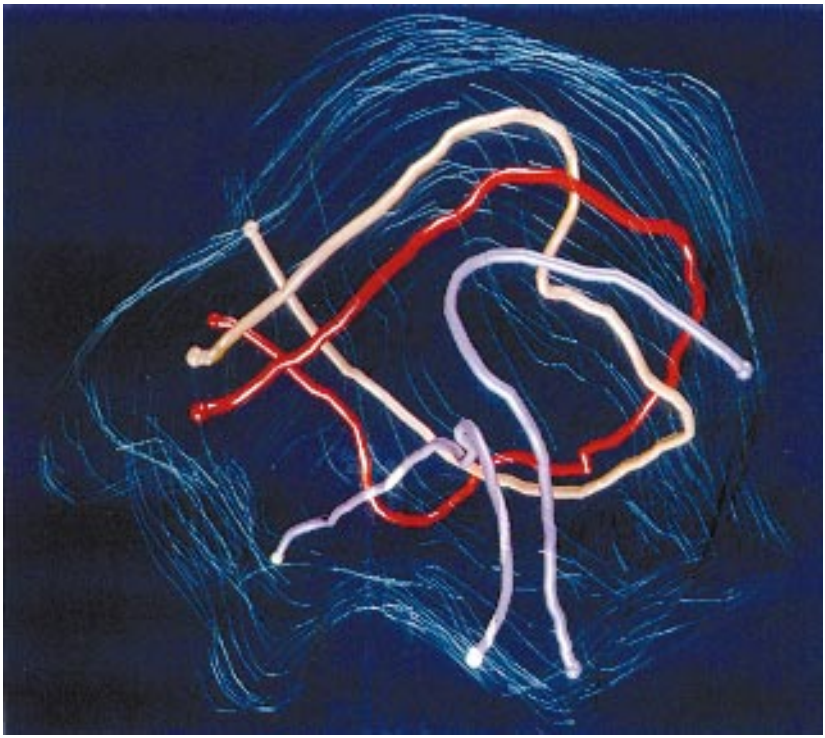


Figure 10 Mid-leptotene nucleus of *Sordaria macrospora*. Three-dimensional reconstruction by computer of two homologues (*pair 1*, red; *pair 2*, pink). Both pairs show colocalization either over their entire length (*pair 1*) or at one distal end with still largely separated telomeres at the other end (*pair 2*). (D Zickler, unpublished data.)

of the nucleus. For organisms with very long chromosomes, this length is only a small fraction of the total length of any given chromosome. For example, as emphasized by Holm (139), in lily, bouquet formation will directly affect the position of only the terminal 10% at each end of each chromosome. The same situation pertains in most plants (1, 130, 146). The limited direct effect of the bouquet within crowded nuclei is nicely illustrated by images of salamanders (Figure 5) (156). This consideration may suggest that the primary role of the bouquet pertains specifically to the behavior of or at chromosome ends. In addition, effects on internal regions of long chromosomes must be relatively indirect. Information could be transmitted from the chromosome ends to other regions in several ways. A signal regarding telomere status could be propagated linearly along the chromosomes from their ends toward their middles. Movement of terminal segments into or out of the bouquet (Figure 7) should create a general stirring of the nuclear contents. For organisms with long chromosomes in a crowded nucleus, this indirect effect will be especially prominent, in counteraction to the more limited direct effect of bouquet formation on internal regions in such cases. Finally, proximity of telomeres to the MTOC could promote chromosome movement directly via microtubule-mediated yanking of chromosome ends (see below).

OUR FAVORITE MODEL As chromosomes emerge from the Rabl configuration into the new condition of early prophase, their "feet" become affixed to the nuclear envelope in a more or less random and dispersed way (see above). Initial contacts between homologues are likely to occur contemporaneously. If so, the feet of homologous chromosomes may frequently become planted far apart from one another. If telomeres cannot move freely around the inner surface of the nuclear envelope at this point, homologue juxtaposition at such ends will be impeded. Thus, if chromosomes ends are to come together properly, the opportunity for fluid movement must be provided at some point. Moreover, as long as sensible coalignment has occurred in interstitial regions, extension of homologue juxtaposition from inward regions outward will tend automatically to place chromosome ends in sensible relative positions, i.e. without interlockings. Movement of chromosomes into and/or out of the bouquet may promote these processes.

This idea emerges from ultrastructural analysis in *Sordaria*, in which the formation of AEs in early leptotene makes it possible to follow the movements of each chromosome at leptotene. In this case, substantial presynaptic alignment seems to be achieved (Figure 10, see color section) without obvious telomere migration toward the bouquet (161, 311; D Zickler, unpublished data). In addition, in several early nuclei, all central regions of homologues are seen to be in contact whereas some chromosome ends are splayed out (Figure 10,

see color section). This description supports the notion that pairing initiates interstitially and also provides evidence that telomere movement within the surface of the nuclear envelope is indeed sufficiently constraining that it actually inhibits or delays extension of interhomologue interactions into terminal regions. In fact, splayed out ends are observed even in late leptotene nuclei where chromosomes have achieved essentially full presynaptic alignment plus a bouquet. Thus, movement out of the bouquet may be as important as the process of bouquet formation. This model can also explain why, in budding yeast (and several other organisms), late zygotene chromosomes have full-length SC except for splayed termini (e.g. 89, 222).

Since the need for membrane fluidity inferred above is driven by the fact of telomere attachment, a question arises: Why attach telomeres to the nuclear envelope in the first place and not simply retain the mitotic configuration of clustered centromeres with relatively loosely attached telomeres? Clustered centromeres should be perfectly conducive to regular chromosome pairing, as occurs in some nonmeiotic cell types that have a Rabl orientation, and emanation of pairing from interstitial regions outward should yield a relatively regular arrangement. Possible answers to this question are considered below.

Does the Bouquet Promote Regular Interhomologue Juxtaposition?

Homologues seem to become intimately juxtaposed via the combined effects of three types of processes: pairing that involves lesion-free chromosomes (160), DNA strand exchange between homologous non-sister chromatids as part of the recombination process, and SC formation. Overall, these processes occur more or less in succession. However, any of the three can be the primary mechanism of homologue contact, at least for some regions of the genome, in some nuclei, for some chromosomes, and/or in some organisms.

THE FIRST INTERHOMOLOGUE CONTACTS CAN PRECEDE THE BOUQUET STAGE

A very common suggestion is that the bouquet configuration is established prior to initiation of homologue recognition and pairing and that this nonrandom organization promotes the initial specific interactions between homologues. In this view, the resultant constrained configuration of chromosomes would reduce the dimensionality of a homology searching process and/or increase the spatial proximity of homologous regions (see 207). It has also been suggested that the bouquet might promote telomere-initiated interhomologue pairing by restricting the freedom of telomere movement, freezing them at the critical moment of their interaction (140).

Despite the attractiveness of these ideas, diverse lines of evidence suggest that homologues have already made initial contact prior to formation of the

bouquet and, in many cases, may actually be substantially colocalized. First, in several fungi, homologues have been shown to recognize each other and align before their telomeres become organized into the bouquet (37, 182, 311, 313) (Figure 10, see color section). Early presynaptic alignment can also be seen at pre-bouquet stages in higher plants and animal cells (reviewed in 176; for recent FISH study, see 256). Second, it is possible to interpret a mid-zygotene bouquet-stage nucleus of lily and other organisms as already exhibiting general colocalization of all homologues into joint domains despite the fact that close juxtaposition (via SC) is present in only a few regions (139). Third, a recent FISH study suggests that during meioses in both mouse and human spermatocytes, homologous loci become intimately juxtaposed concomitant with bouquet formation and that this configuration is achieved by a very rapid transition from a configuration in which homologous loci are much farther apart (253). The apparent rapidity of this transition again forces the suggestion, raised by the authors, that the major work of homologue pairing has already been completed before this transition occurs. These authors suggest that initial contacts between homologues might occur in interstitial regions when chromosome ends are attached to the nuclear envelope and that migration of chromosome ends into the bouquet would then promote these chance contacts. An apparently analogous rapid transition has been observed in maize in which pairs of homologues become juxtaposed at the leptotene/zygotene transition, essentially concomitant with bouquet formation (25, 74), though these authors do not favor the idea of earlier contacts. Finally, in budding yeast, homologues are paired in G1/G0 prior to meiosis, but this premeiotic pairing is temporarily disrupted during meiotic DNA synthesis and then reestablished, probably before the formation of DSBs, which in turn occur during leptotene, prior to the knot and bouquet stages (298) (see above).

SC formation often first initiates subtelomerically (292). Also, the process of pre-SC homologue pairing might be specialized at or near telomeres (e.g. 128a, 173, 174, 257, 298). The SC findings have sometimes been cited as evidence that the bouquet configuration promotes pairing directly by promoting juxtaposition at or near ends. But the pattern of SC formation may reflect the timing of later processes; similarly, functional specialization at chromosome ends need not imply any particular temporal specialization. Furthermore, for long chromosomes, pairing of telomeres would have little direct effect on the relative positions of homologous interstitial regions (see above). Early interhomologue contacts could initiate exclusively in telomeric or near-telomeric regions and then propagate progressively inward toward the middles of the chromosomes, but without additional assumptions, this scenario would be likely to result in massive interchromosomal entanglements in the middles of chromosomes (e.g. 161, 239a). Initiation of early homologue pairing in interstitial

regions followed by progression toward terminal regions could be more attractive (see below).

Effective homologue coalignment clearly can occur in the absence of a bouquet configuration. An appropriate pairing process could, in principle, draw homologues together progressively all along their lengths irrespective of any prior spatial proximity (161). Also, the informational and spatial complexity of the homology search process can be reduced irrespective of the bouquet. If each initial contact between homologues is followed by their rapid colocalization into a joint space, each such event will reduce the complexity of the remaining searches, which will occur more and more rapidly as the process progresses (for precedent, see 44). And finally, pairing occurs in somatic and premeiotic cells of some organisms; where present, the Rabl orientation likely contributes, however (e.g. 105).

DOES THE BOUQUET HELP AT INTERMEDIATE STAGES? Our favorite model invokes a role for the bouquet in dealing specifically with terminal regions of the chromosome after substantial colocalization has occurred elsewhere. Similar proposals have been suggested by others with the significant difference that the bouquet is suggested to play a more prominent role for all regions of the chromosomes rather than addressing the specialized needs of terminal regions.

Homology searching Scherthan et al (250, 252, 253) suggest that the mature bouquet configuration could promote occurrence of interhomologue contacts in more distal regions (i.e. farther toward the chromosome ends), by the fitting together of pairs of U-shaped chromosomes. The possibility has also been raised (M Lichten, personal communication) that the bouquet acts at an intermediate stage, suggesting that perhaps one or a few "kisses" (pre-DSB pairing contacts), plus bouquet formation, might suffice to bring homologues close enough together that recA-promoted homology searching and strand exchange, plus SC formation, could proceed efficiently; for a similar idea see Moens and colleagues (202a). These more extreme scenarios are clearly not applicable in organisms where essentially full coalignment is achieved prior to the bouquet stage, nor do they seem likely in organisms with very long chromosomes.

Avoiding or eliminating entanglements Chromosomal interlocking can be detected in zygotene nuclei from various organisms (reviewed in 293). In addition, there is the potential for formation of internal knots within a single chromosome or involving multiple chromosomes (146). The bouquet has often been proposed as helping in the minimization of chromosome interlocking, either by placing homologues in a more favorable relative conformation before they become connected or by providing a more favorable topology near the ends of the chromosomes (176, 250, 253). With regard to models of the latter class,

however, an important distinction must be made. Bending of the chromosome array per se, e.g. into the general U-shape of the bouquet, should not change any of the component topological relationships, so migration of an entrapped chromosome out the end of an entrapping bivalent will involve the same topological changes regardless of whether the chromosomes are straight or bent. Thus, the presence of the bouquet should not directly influence the process of interlock resolution. On the other hand, the act of movement into or out of the bouquet could well be important, either actively or passively (see below). Interestingly, some images seem to suggest that homologues that fail to become colocalized prior to bouquet formation are then drawn into the bouquet and undergo telomere-proximal SC formation, thereby encircling and entrapping regularly paired bivalents (139, 239a). In this case, the bouquet would create, rather than help to resolve, interlockings. One is again tempted by the notion that interlock resolution is promoted by release of the bouquet configuration rather than by its formation or existence.

PROMOTING SC FORMATION? The bouquet configuration has for many years been tied to initiation of SC formation by two types of observations: (*a*) SC formation begins while homologues are in this configuration (reviewed in 81, 114, 176, 207, 293); and (*b*) in many organisms, SC formation is mainly initiated subtelomerically; moreover, in several species SC zips up exclusively from these subtelomeric sites (reviewed in 293). Progression of synapsis from the telomeres inward into the mass of chromosomes is indeed clearly seen in Kezer et al (156) (Figure 5). How can these findings be evaluated and understood?

First, neither a temporal nor a spatial relationship between the bouquet and SC initiation necessarily implies a functional dependency of SC formation on occurrence of the bouquet. The temporal correlation could reflect a coordinate response of both processes to a common signal. Similarly, a spatial correlation could reflect a tendency for relevant preceding processes to occur earlier, or in a special way, in near-terminal regions, irrespective of clustering of ends in a bouquet region. For example, there is sometimes a spatial and temporal relationship between telomeres and axial element development: In human and *Bombyx* spermatocytes, AEs appear at envelope-associated chromosomal telomeres earlier than in interstitial regions (36, 238, 240). Perhaps early SC formation reflects early AE development, or perhaps initiation of SC formation is promoted by appropriate morphogenesis of interstitial interhomologue interactions, with the critical transition tending to occur first or earliest in near-terminal regions (see below). AE development and progression of interstitial interactions (and, thus, SC formation) might both respond to a single common signal.

Second, bouquet formation is not sufficient for SC formation. A bouquet is seen in tomato mutants defective for SC formation (131). Similarly, telomeric

DNA sequences are not sufficient for SC formation: Telomeric repeats that occur internally on the chromosome do not lead to synapsis with the telomerically positioned repeats (reviewed in 116).

Third, the bouquet is also not absolutely required for SC formation. In many organisms, several SC initiation sites are found along the different bivalents in the same time or even before telomere SCs, clearly demonstrating that SC can be initiated outside of the bouquet (Figure 7) (e.g. 1, 7, 115, 130, 139, 271 and references therein). Moreover, 3D reconstructions indicate that the occasional bivalent ends not attached in the bouquet area can, nevertheless, synapse (238). And finally, ring chromosomes show perfect synapsis (188).

Fourth, nonetheless, if bouquet formation promotes regular homologue juxtaposition (see above), it may promote SC formation by permitting its extension into terminally (or interstitially) blocked regions.

SPECIAL HELP FOR LATE-STAGE PROBLEMS? The bouquet stage can serve as final backup mechanism for promoting the juxtaposition of homologues that have failed to become colocalized previously via the normal route. This might not be the primary role of the bouquet, but it could still be a significant advantage. This possibility seems clearly true in triploid *Bombyx* females and rainbow trout (219, 239) (see above). In those cases, release of bivalents from the bouquet seems relatively coordinate, but there is a clear differential response of bivalents and univalents to the "exit bouquet" signal. The mechanism of this biphasic release, and the signal that differentiates synapsed from unsynapsed chromosomes, is unknown. Similarly, in the case where the bouquet actually creates an entanglement, as depicted above, it would be the act of bouquet formation that serves as a last-ditch mechanism for homologue colocalization, but with the concomitant necessity of dealing with resulting topological complications.

Scherthan et al (253) also suggest that the bouquet promotes pairing of leftover chromosomes by providing for their spatial segregation, via a rather dynamic process: "Once connected, paired homologs will rapidly relocate from the cluster site [while] as yet unsynapsed partners remain at the cluster site where a reduced number of encounters facilitates the pairing of the remaining ones." The latter mechanism would apply, of course, irrespective of the bouquet: In regions of the chromosomes where pre-SC mechanisms for homologue juxtaposition have failed to occur, SC formation, rather than early homologue pairing or DNA strand exchange, could be the only process involved in bringing together leftover regions. But spatial proximity of AEs provided by the bouquet configuration might promote such synapsis. Similarly, the bouquet could stimulate SC formation in situations where underlying chromosomal homology is totally absent. This would seem likely in the case of late SC formation involving univalent chromosomes at the bouquet stage in *Bombyx* and trout triploids (see

above) and could analogously be true in haploid meioses where SC forms between nonhomologous chromosomes (112, 178) and where bouquet formation occurs (76, 249, 297).

REESTABLISHMENT OF NUCLEAR ORDER FOR SUBSEQUENT CHROMOSOME SEGREGATION In mitotically cycling cells, the Rabl orientation is preserved after telophase through to the subsequent G2 phase (see above) and then reinforced by the process of mitosis itself. This continuity presumably helps to ensure the orderly congression of chromosomes to form the spindle at the next mitosis and also contributes to other cellular processes that depend on specific chromosome organization within the nucleus, such as gene expression (e.g. 80, 85). In meiotic cells, however, the Rabl configuration is disrupted prior to or during early meiotic prophase (e.g. 148); moreover, the process of chromosome pairing will tend to induce nuclear disorder (see below). Thus, perhaps the bouquet could be part of a multistep program used to reestablish overall chromosomal order within the nucleus, following the major work of chromosome pairing. Such a process should be a prerequisite to orderly chromosome congression at meiosis I and perhaps for other reasons developed below. Establishment of cell polarity is a central feature of morphogenesis in many types of cells, why not in meiocytes?

Reestablishment of order could involve the following stages. First, bouquet formation would reestablish chromosomal polarity, with telomeres toward one end of the nucleus and centromeres more or less toward the other end, albeit with an orientation to the MTOC/SPB that is inappropriate to the ensuing division. Then, when chromosome ends disperse around the nuclear periphery at pachytene, centromeres will tend to remain centrally localized [as seen dramatically in *Drosophila* (50)]. In this configuration, telomeres release from the nuclear envelope at late pachytene/early diplotene but remain otherwise more or less in the same dispersed centromere-central configuration as during mid-pachytene (e.g. 140). From this configuration, microtubule attachment to kinetochores can occur in a regular way. In essence, reestablishment of order during meiotic prophase takes advantage of aspects present at the appropriate moment, i.e. embedding of telomeric ends in that envelope plus the ready possibility of nuclear envelope polarization. Each of these features could still have its own individual importance, independent of the bouquet, e.g. to minimize interlocking or to promote repolarization of other nuclear envelope contents as part of an overall development of nuclear and cell polarity (see above). Also, some features, such as the Golgi clustering around the centrosome that establishes the cell polarity of mammalian meiocytes, are already present before the bouquet stage, indicating that the bouquet does not trigger this polarity but is more likely part of a general cellular reorganization (240) (see above).

Creating New Possibilities for Order-Dependent Gene Expression

Although no data indicate a role of the bouquet in gene regulation, it could play such a role. Several data from *Drosophila* and human suggest that, for nonmeiotic cells, particular regions of the genome tend to occur at particular positions within the nucleus and show that the organization of homologues or chromosome regions in a nucleus can influence the pattern of expression of their corresponding genes (see 80, 192). Data from nonmeiotic cells also indicate that interactions between homologous regions can occur and can influence gene expression and, potentially, other processes (12, 70, 80, 85, 93, 154, 171). The meiotic bouquet might influence these types of effects. Moreover, because it creates a polarized centromere/telomere organization unique to this stage, the bouquet could serve to limit unwanted conditions and/or to facilitate associations of chromosomal regions that normally are not associated. The overall effect might be to activate (or deactivate) genes normally repressed (or activated) in nonmeiotic cells, where telomeres are generally more dispersed.

One prominent possibility is that placement of the nucleolus to the nuclear periphery concomitant with bouquet formation could promote movement of rRNAs into the cytoplasm during mid-prophase. Also, to the extent that it promotes homologue association, the bouquet will promote the formation of robust contacts between homologous regions instead of those present in nonmeiotic cells, which can be rather weak (e.g. 171). Interhomologue contacts during meiosis are stabilized in part by DNA strand exchange, and one mechanism by which homologues could "talk" was suggested to implicate direct interactions between nuclease-sensitive regions, which are also often the regions in which meiotic DSBs occur (155, 218, 304).

CHROMOSOME MOVEMENT, ACTIVE AND PASSIVE

Rotational/Curvilinear Motions During Meiotic Prophase in Animals

Cine-micrographic studies of cultured rat spermatocytes reveal rotational and oscillational motions that occur specifically at mid-prophase (228, 248). No motion was observed before late leptotene; motion was most active at early zygotene, decreased through late zygotene, and ended during early pachytene. Movements were variable with respect to both speed and direction. Rotary motion occurred at $\sim$2.5–3 μm per minute, faster than that usually associated with poleward movement at anaphase, with directional changes occurring over time intervals of less than a minute. Although the general impression is of an overall rotation of the entire nuclear contents, the chromosomes were judged to

be moving "around several axes in numerous different planes" (228) and also to rotate relative to one another (248).

Nuclear rotations with saltatory motion have also been described in cricket spermatocytes at diakinesis (243). Chromosomal motions resulted from application of force to localized regions of the bivalent, most of which moved passively in response. Frequently it was the telomere and occasionally the kinetochore regions that led the movement. Active ends and kinetochores are associated with the nuclear envelope and maintain this association throughout a movement, with accompanying morphologies suggestive of chromatin stretching at the site of association. In contrast, chromosomal regions within the center of the nucleus did not move. In any case, the movements are independent of overall rotation of the nucleus as a whole, because adjacent chromosomes, including two nearby chromosome ends, can move independently. Interestingly, nuclear motion seen in nonmeiotic mammalian cells maintained in vitro seems also to be prominent in certain cell types or under certain, perhaps transitional, conditions (reviewed in 75), and as in cricket, the motions could be seen to reflect motion of chromatin domains rather than motions of the nucleus as a whole.

Several findings suggest the involvement of microtubules in the meiotic motions observed. The microtubule inhibitor colchicine at moderate concentrations slowed this motion; at very high concentrations, motion stopped. In contrast, a non–MT-binding derivative of colchicine, lumicolchicine, had no effect (243, 248). In the cricket study, the asters are implicated directly, both from the specific nature of chromosome motions ["into (or away from) a center"] and from the fact that aster-associated cytoplasmic granules exhibited movements similar to those observed for the chromosomes. The idea of MT involvement has, nonetheless, met with resistance. For rat spermatocytes, two other inhibitors, vinblastin (MT) and cytochalasin B (microfilaments), had little or no effect on motion. This could be due to lack of permeability; alternatively, colchicine might exert its effects in some other way, e.g. via damage to the nuclear membrane, which was obvious at very high colchicine concentrations (248). In the cricket case, the notion that the asters are the force producers was deemed unlikely because it would require molecular interaction between MTs and chromosomes across the nuclear envelope, and an actin/myosin system was considered. Intranuclear actin/myosin motor and/or extranuclear, cytoplasmic, actin-based motor were suggested as driving the motions seen in mammalian cells (reviewed in 75). Regardless, SPB-directed yanking of meiotic fission yeast chromosomes implicates astral MTs (reviewed in 163) (see below). Thus, the possibility of aster-directed movements for animal chromosomes might merit reconsideration, albeit with stochastic susceptibility of individual chromosomal regions within the complement.

Back-and-Forth Chromosome "Yanking" in Fission and Budding Yeasts

During meiotic prophase of both zygotic and azygotic meiosis of *S. pombe* and other *Schizosaccharomycetes*, the nucleus is dramatically elongated (the "horsetail" stage), and chromosomes undergo strong nuclear movement between the cell poles, a distance of 5–10 μm (17, 53, 276). These motions, which continue for 2–3 h, are led by the SPB and the telomeres, which become associated with the SPB prior to meiosis and are sensitive to MT inhibitors; thus, it is suggested that this movement involves microtubules (17, 53, 276). These nuclear migrations are accompanied by characteristic configurations of astral microtubules (53, 276). In addition, cytoplasmic MTs extend from this position toward the two poles of the cell. This configuration is specific to the period when movements occur; thereafter, the nucleus is arrested in the center of the cell, and the two poleward MT arrays disappear (276). Yamamoto et al (305a) showed that disruption of a cytoplasmic dynein heavy-chain gene disrupts this nuclear movement, without disrupting microtubule organization, which suggests that dynein may be the molecular motor responsible. Alternatively, Svoboda et al (276) propose that chromosomal movements are mediated by coordinate shortening and lengthening of the two poleward MT arrays and suggest that the nucleus is pushed toward, rather than pulled by, the SPB. Two mutants, *lot2* and *lot3*, defective in the ability to impose transcriptional silencing on telomere-located genes, also show reduced horsetail movement: In the absence of telomere associations with the SPB, telomeres remain in the center of the nucleus whereas the nuclear envelope shows some yanking (214).

Nuclear movements have also been detected during mid-meiotic prophase in budding yeast (131a). These movements are much less dramatic than those observed in fission yeast but could be roughly analogous. Interestingly, the budding yeast chromosomal mass can be rather elongated at leptotene (222) (Figure 3*f*); perhaps this is a less exaggerated version of the fission yeast horsetail configuration. An SPB-led back-and-forth motion of chromosomes has also been observed in vegetative budding yeast cells at the point when the nucleus is elongated between the mother cell and the bud (225, 226). This behavior, referred to as nuclear transits, is rare in normal exponentially dividing cells but is common in a number of mutants that arrest at the appropriate stage. Furthermore, these movements are strongly dependent on astral microtubules, which, at the relevant stage, extend from one pole of the spindle into the bud and from the other pole of the spindle into the mother. This process does not require the *KAR3* gene, one known MT-associated motor protein that is somehow important for meiosis (see below). These mitotic transits would seem to be analogous to those observed in fission yeast meiotic prophase except that

(*a*) the extent of SPB movement is likely much less (1 rather than 5–10 μm) and (*b*) the mode of attachment of chromosomes to the aster/SPB complex seems to be via the centromeres rather than via the chromosome ends.

Constrained Local Motions in Nonmeiotic Cells

DURING PLANT MITOSIS Cine-micrographic studies of mitotic prophase in endosperm of several plants reveal relatively little motion of chromosomes, with Brownian motion and changes in chromatin compaction suggested as explanations for the motion observed (e.g. 18, 19). In certain exceptional cases, however, late prophase "chromosomes move conspicuously, oscillating irregularly without shifting far or causing the general arrangement of the group to change" (18). Whether these motions are directed or reflect higher order chromosome compaction is unknown.

MOVEMENT OF CHROMOSOME DOMAINS IN INTERPHASE CELLS Two recent studies have shown slow chromosomal motions in mammalian interphase cells (for review, see 315). Shelby et al (258), using green fluorescent protein (GFP)-tagged centric heterochromatin, report that centromeres are primarily stationary; however, motility of individual or small groups of centromeres occurred occasionally, at very slow rates (0.1–0.2 μm per min). Zink and colleagues (314, 315), utilizing BudR-labeling of individual chromosomal regions, report similar selective, slow movement of whole territories. Explanations for such motions include the following: stochastic fixing of regions, to an intranuclear structure or to another chromosome, with reverberations along the lengths of the chromosome(s) in the vicinity of the contact; reverberating effects of a local change in chromosome compaction; or occasional yanking on a chromosome via cytoplasmically located forces via attachments to the nuclear envelope.

Marshall et al (193) have been able to quantitate diffusional motion of specific loci in living diploid cells of both yeast and *Drosophila* and showed that a given interphase chromatin locus is confined within a small subregion of the nucleus. In yeast, the distances between GFP signals at allelic positions on homologues were measured in G1 cells. The distribution of distances observed over short time intervals implied a random walk process corresponding to linear motion of $\sim$0.02 μm/s, which likely reflects Brownian motion (not inhibited by azide, which blocks essentially all cellular processes). The distance distribution observed over long time intervals, however, implied that the monitored sequences were constrained to move within a limited region, of radius $\sim$1% the nuclear volume. Interestingly, confinement is disrupted by nocodazole treatment, suggested to reflect involvement of microtubules. Perhaps centromere clustering is disrupted by nocodazole: The locus analyzed is located near a chromosomal centromere, and in yeast, centromeres are known to be clustered

in a Rabl orientation during the G1 phase (148). A similar situation is inferred to exist in *Drosophila* embryo nuclei from analysis of specialized foci of topoisomerase II immunostaining obtained by microinjection of cognate antibodies. The diffusion constant was similar to yeast, and the area of confinement was slightly greater (0.9 μm), with similar possibilities for sources of the confinement. Homologues in both *Drosophila* embryos (193) and in yeast diploid G1 cells (S Burgess, B Weiner, personal communication) are paired via multiple interstitial interactions; perhaps these interactions also constrain chromosomal motion.

PASSIVE SOURCES OF CHROMOSOME MOTION IN MEIOCYTES Normally occurring events in the meiotic prophase nucleus will tend to perturb chromosome position. First on the list of such events is chromosome pairing. Assuming that pairing involves stabilization of chance contacts between homologues (e.g. 105, 161), any time a contact is made between homologues, the presence of that contact, for whatever its lifetime may be, will constrain the random movements of adjacent segments, thus resulting in a change in relative chromosome disposition. Second, assembly of chromosomes into linear loop arrays should tend to cause motion, with the resultant pulling of each sister pair into its own, more limited, spatial domain. Likely to be more important, however, is the extension of linear loop arrays via stiffening of the chromosome axes, before, after, or because of AE formation. Third, movement might also be promoted by changes in the degree of compaction of bulk chromatin and/or of the status of sister chromatids, as occur during meiotic prophase (see below) (e.g. 74, 90, 207, 222, 252, 253). Fourth, the act of attaching chromosome ends to the nuclear envelope during leptotene will result in the repositioning of chromosomes in the accommodation of the new constraint. Finally, the process of bouquet formation, however driven, will also create motions, not only at the chromosome ends but also in their middle regions; a conspicuous case would be the centromere regions of all chromosomes with one long and one short arm, which must readjust positions dramatically between the Rabl and the bouquet configurations. For organisms with flexible chromosomes, and/or given a viscous intranuclear milieu, such readjustments might be relatively minor and confined primarily to regions near the bouquet-end of the nucleus (see above). For organisms with shorter or stiffer chromosomes, motion of the ends and separation of the centromeres will have a greater effect. It may be noted that the longest and shortest chromosomes, e.g. in lily and in yeast, might nonetheless behave similarly given the not unlikely especial flexibility of yeast chromosomes.

HARMONIC OSCILLATIONS: THEORETICAL APPROACHES Faberge (99) applied the Guyot-Bjerknes effect to meiotic chromosomes. Essentially, two vibrating

objects (e.g. two balloons suspended on a water surface and undergoing rapid reversible inflation or deflation) attract one another if they are expanding and contracting in phase and repel one another if they are expanding and contracting in opposition. This behavior is a consequence of Bernoulli's theorem (see Faberge's lucid description). Faberge suggested that homologous chromosomes might attract one another by virtue of having their own specific, phased vibrations. This specific application of the analogy no longer seems likely. However, a more generalized version of this notion could have some relevance. Expansion and contraction of relatively condensed (e.g. leptotene or later stage) chromosomes would tend to provoke chromosome motion and, if synchronous, would tend to promote the general coalescence of chromosomes within the nucleus. There is some evidence for repeating nucleus-wide cycles of expansion and contraction (e.g. 222) (see below). These would represent very "long wavelength" vibrations, but the basic principles put forth by Faberge should pertain for even a single cycle of expansion or contraction.

Of (perhaps even more) tangential relevance is the argument of Pienta & Coffey (230) that cells and intracellular elements are capable of dynamic vibration with complex harmonics. Specifically, vibrational information originating at the cellular periphery (e.g. ruffling) might be transferred through a tissue matrix, comprising the extranuclear matrix, the cytoskeleton, and the nuclear matrix, to the DNA/chromosomes within the nucleus, thereby influencing gene expression (or presumably, in the case of meiosis, other aspects of chromosome behavior, such as chromosome motion). No direct experimental link with any aspect of meiosis has been made, however.

Possible Roles for Chromosome Movement in Meiotic Prophase Chromosome Morphogenesis

Chromosome movement, however generated, could provide a "stirring force" (187) that increases the probability (per unit time) that homologous regions of the genome will happen to be in the same place in the nucleus at the same time. This could be important for initial contacts or for continued propagation of initial contacts to other regions.

Back and forth motions, linear or rotational, could help with resolution of entanglements. Such motion alternately places the chromosomes under a force that tends to extend them and then causes the chromosomes to move back on themselves, which then causes extension again, etc, just as does an alternating pulse field gel for individual DNA molecules. This type of motion is exactly what one might require to "loosen up" a tangled rope, permitting release of certain other types of entanglements, e.g. an internal loop of one chromosome entrapped by a homologue pair or a knot within a single chromosome, much as shaking a tangled garden hose or a knot of yarn might promote loosening

of internal knots or disruption of unstable/incorrect contacts. Also, in some scenarios, the fact of chromosome movement per se could help to drive resolution of interlocks, in interstitial as well as terminal regions. For example, consider a case where one chromosome is entrapped interstitially within another prior to the formation of permanent interhomologue connections on both sides: Movement of the entrapped chromosome by one-dimensional random walk will, eventually, and given fluidity of movement of chromosome ends within the nuclear envelope, result in walking of the entrapped chromosome off one end or the other of the entrapping chromosome. In this scenario, any event that increases either the "step size" of such a random walk or the rate of walking (in axis length per unit time) will promote interlock resolution.

A less obvious possibility is that yanking or shaking motions could be important for getting the kinks out of chromosomes, ensuring development of smooth, regular chromosome axes. There is some evidence in yeast for a discrete "snapping together" of chromosomes as a final stage in axial morphogenesis; motion might help with such a transition. And if this transition were also important for progression of recombinational interactions, and/or for the decision as to whether interactions will be resolved as crossovers or noncrossovers, such motions could affect these processes as well.

Actual information bearing on the role of chromosome movement for chromosome behavior is scarce. Reestablishment of somatic pairing contacts could be such an example. In a stage 13 *Drosophila* embryo transiting mitosis, homologue pairing is strongly reduced, and when pairing at a particular assayed locus is reestablished, the motion involved fits closely the predictions for a random diffusion process (see above) (105). Pairing in this case is likely greatly facilitated by the presence of the Rabl configuration and other features that constrain intranuclear chromosomal position (192). It remains to be seen, however, whether diffusion suffices for meiotic homologue pairing or whether stirring forces are also required. Also, two types of evidence provide at least a circumstantial indication that actively driven chromosome movement could play an important role. Microtubule inhibitors and mutations that reduce or abolish chromosome yanking in fission yeast can affect leptotene/zygotene chromosome movement, bouquet formation, meiotic recombination, and/or SC formation, though these findings all have alternative interpretations. For further discussion, see the following section and previous considerations (e.g. 53, 81, 105, 163, 176, 248, 250, 251, 253, 276).

TELOMERES AND RECOMBINATION

Introduction

A number of observations have raised the possibility that the frequency or nature of meiotic recombination is affected by events involving telomeres. In

evaluating the nature of recombination, in normal or variant situations, several issues recur.

First, it is generally assumed that if two regions are not sufficiently near one another, they will not recombine efficiently; in cytological parlance, prior "pairing" is assumed to be required for recombination. Two extreme scenarios are possible: (*a*) coalignment of homologues in the absence of recombination initiation, followed by DSB formation and homology searching via recA homologues, or (*b*) rough coalignment via diverse features not involving direct contact between homologues followed by progressive coalignment mediated primarily by strand exchange (for potential problems with the latter scenario, see 161). A related issue is the mechanistic one of whether relative chromosomal position determines recombination frequency. For example, if recombination is initiated by a DSB on one chromosome, that DSB might, given sufficient time, always be able to find its homologous partner region, irrespective of relative chromosomal position. Also, if recombination does sense relative chromosomal position, the question then becomes which step of the recombination process is sensitive to the relative local concentrations of the interacting partners. Is it the formation of the DSB itself, which would then occur only in response to a prior interhomologue contact? Or is it, as seems most straightforward, the ability of DSB ends to identify an homologous region? And if so, what happens to the DSB if it fails to find an interhomologue partner in time? Is the sister chromatid accessible? Is the corresponding chromosome lost?

Second, a recombinational interaction can give one of two possible outcomes: a crossover, in which there is an exchange of the flanking chromosome arms, or a noncrossover, in which molecular changes occur in the DNA at the site of the interaction but the flanking arms remain in their original relative positions. The distinction between these two outcomes is crucial for meiosis because a crossover (plus sister connections and maybe other features) can promote homologue disjunction whereas a noncrossover cannot. In some organisms, notably yeast, something like half of all recombinational interactions yield crossovers. In other organisms, however, crossovers may comprise only a tiny fraction of all interactions. In *Allium*, for example, the number of early zygotene nodules is 50 times higher than the number of crossovers (7), and these nodules likely correspond to the sites of (all) DSB-initiated recombinational interactions (see below). Crossovers and noncrossovers likely occur as alternative branches of a single primary pathway (255, 272).

Furthermore, the final distribution of crossovers between and along chromosomes is determined by a crossover control "process" (e.g. 49, 153, 160). An oversimplified view is that this process involves two components. First, each pair of homologues must receive at least one crossover, as required for their disjunction at meiosis I; this feature is referred to as occurrence of the "obligate" crossover. Second, if two or more crossovers occur along a single

pair of homologues, these are as far apart from one another as possible; this is the phenomenon of "crossover/chiasma interference". These two outcomes appear to reflect a single common process because they are often lost coordinately in variant situations (49, 52, 150, 273, 278). A particularly striking example is that of two contrasting rye genotypes, one of which exhibits normal crossover control whereas in the other the distribution of crossovers between and along chromosomes follows the Poisson distribution (150). The occurrence of crossover interference has been inferred from both genetic studies (e.g. 169) and cytological studies (61, 153). A common assumption is that recombinational interactions begin but are initially undifferentiated until they are acted on by the crossover control machinery, and that those interactions not designated for maturation as crossovers are matured as noncrossovers.

In many studies, recombinational events are detected by assaying only crossovers, genetically (274), cytologically as chiasmata (152, 153) or late nodules (52, 312), or physically (40, 223). However, a defect in crossover formation could, in principle, reflect a defect in the occurrence of total events, a defect specifically in maturation of events destined to be crossovers but not of events destined to be noncrossovers, and/or a defect in crossover control. The total number of recombinational interactions may be estimated, at least approximately, by several assays: (*a*) DSBs, (*b*) early nodules (see below), (*c*) intragenic (heteroallelic) recombination, which usually reflects the occurrence of a strand invasion and heteroduplex DNA in the immediate vicinity of the assayed locus irrespective of whether that interaction is resolved as a crossover or a noncrossover, or (*d*) in specialized constructs by physical analysis (211, 272).

Third, the recombination reaction as studied in yeast appears to progress through three specifically programmed transitions: formation of a resected DSB, conversion of that DSB to a double Holliday junction, and resolution of such junctions into products (160, 245, 266). A defect at any step in this process could disrupt either (*a*) biochemical progression through that step, reducing the probability that two intact duplexes will emerge at the end, or (*b*) the qualitative normalcy of that step with regard to one or both aspects of crossover control. Thus, subtly different perturbations of some single step might have dramatically different effects on the number and/or distribution of crossover and/or noncrossover events.

Timing of the Events of Recombination Relative to the Bouquet Stage

DNA EVENTS Bouquet formation and disappearance are approximately contemporaneous with crucial intermediate events of meiotic recombination. Studies in three organisms suggest that DSB formation probably precedes the

bouquet stage. In budding yeast, in a direct comparison, DSB formation occurs at leptotene, concomitant with the presence of short axial element segments (223) and prior to both a synizetic knot stage, and the obvious zygotene bouquet stages (222). In *Sordaria*, Dmc1 and Rad51 immunostaining foci, which likely mark the positions of meiotic DSBs (see below), appear on chromosomes already substantially coaligned but prior to the bouquet stage (D Zickler, unpublished data). And in mice, short AE (Cor1-staining) segments show associated Rad51 foci at leptotene (201, 202a). Double Holliday junctions seem to appear at zygotene/early pachytene (223, 254) and, thus, probably during and after the bouquet stage, an idea also supported by changes in early nodule morphogenesis during this period (see below).

In yeast, the DSB to double Holliday junction transition is approximately contemporaneous with the onset of SC formation and SC polymerization (254), i.e. contemporaneous with what is universally the time of the bouquet stage. Mature recombination products appear at about the end of pachytene, almost certainly after release of the bouquet (222, 223).

CROSSOVER CONTROL The only information on the timing of crossover control comes from analysis of recombination nodules. Early nodules (ENs) are many in number and occur all along the lengths of the chromosomes at late leptotene/zygotene/early pachytene, according to the organism, and apparently correspond to DSBs and, thus, total interactions (10, 21, 34, 35, 109, 201). Late nodules (LNs) correspond in number and position to crossovers, implying that they mark the sites where crossovers will occur, are occurring, or have occurred (49, 51, 52). Given this situation, originally proposed by von Wettstein et al (293), the timing of the transition from early to late nodules places constraints on when the differentiation of recombination intermediates into crossover and noncrossover classes might occur. The point of transition between the two forms provides a "latest time" at which the crossover control decision might have been made. Rigorously, differentiation must occur no later than the time of the first transition observable morphologically, but it could have occurred at any earlier point in the absence of a morphological correlate.

In most organisms, the ENs disappear abruptly at the end of zygotene and/or at early pachytene and are not seen in fully synapsed nuclei (8, 262, 271). In several organisms, the two types of nodules appear successively. Sometimes only one type can be seen during a given part of prophase, e.g. in higher plants, ENs are confined to zygotene (e.g. 7, 271), whereas in *Drosophila*, LNs are present only during pachytene (51). In other organisms, however, both types of nodules overlap during early pachytene, with ENs dominating at zygotene and LNs more frequent at pachytene (reviewed in 52, 293). For example, in *Sordaria* and *Neurospora*, LNs appear during midzygotene, and their number increases

until midpachytene and stays at that level (the same as the number of chiasmata) until diplotene; ENs appear at early zygotene with the first association sites, increase in number during zygotene, and are steadily eliminated during early pachytene (38, 312). The transition from a large number of ENs to a smaller number of LNs can occur as early as midzygotene, as seen in *Sordaria* and *Neurospora* (38, 312). And the timing of this transition may well be just as early in other organisms. In tomato, the morphological transition from early to late forms occurs at early pachytene (262), but the differentiation of early morphology nodules into two stability classes, which could be an earlier sign of differentiation, occurs during zygotene (261a). Finally, most organisms show early nodules of different shapes, which could correspond to transition stages (e.g. the DSB to double Holliday junction transition), and in many organisms, the reduction in nodule number occurs at, or close to, the end of zygotene (293), which implies that the morphological changes occur prior to that point (i.e. prior to when double Holliday junctions should be present).

These findings imply that crossover/noncrossover differentiation at the DNA level should occur no later than the time of double Holliday junction formation, rather than at the time of double Holliday junction resolution. And since the morphological consequences of the decision might be expected to take some time after the decision is actually made, these findings might hint that the decision occurs during exit from the DSB stage or during the early stages of double Holliday formation rather than after double Holliday junctions are molecularly complete. It is also possible that the decision is made much earlier. Because there is a delay between the occurrence of double Holliday junctions and the appearance of mature recombination products, an important implication of this timing is that there may well be both "establishment" and "maintenance" phases for crossover control. Molecular models for crossover/noncrossover differentiation can accommodate this timing. The point of differentiation at the chemical level is traditionally placed at the point of double Holliday junction resolution (137, 245, 279), in which case double Holliday junctions must be marked well in advance of the actual resolution step. Another model, however, argues for differentiation as a function of the geometry with which DSB ends invade an intact duplex, i.e. exactly at the DSB-to-double-Holliday-junction transition point (273; see also 267). It is also not rigorously excluded that crossovers go via double Holliday junctions whereas noncrossovers go via another route (e.g. 212), as pointed out to us long ago by DK Bishop and more recently favored by JE Haber, personal communications).

Another implication of this timing would be that implementation of crossover control does not require full-length SC, as in some models (158). Other models suggest that some aspect of the recombination process determines the obligate crossover, and then a kinetic race between SC polymerization and initiation of

further crossovers determines interference (94, 95, 245). [The post-SC model (158) also uses this same logic but via a different mechanism for interference.] Another model suggests that both aspects of crossover control are implemented via the imposition and relief of stress along chromosomes, via basic structural features (160, 273; N Kleckner et al, manuscript in preparation) (see below). In this model, kinetic parameters are irrelevant. In addition, the SC might also be irrelevant; or alternatively, it might play an "implementation" role, being mechanistically required, but in response to, rather than as the primary "designator" of interference. In any case, chiasma determination is not necessarily sequential along the chromosomes (151, 153).

GENETIC INSIGHTS FROM BUDDING YEAST *Probing chromosome position using recombination* Goldman & Lichten (118 and personal communication), using a specific recombination reporter construct pair that allows pairs of alleles to be placed at desired position in the genome, showed that recombination is highest when the two loci are present at allelic positions on homologues, and intermediate when present at two different positions on homologues, versus when present on two nonhomologous chromosomes. In the latter case, however, recombination is higher when the tester constructs are present near their respective telomeres than when present in nontelomeric locations or when one construct is telomeric and the other not. These results imply that recombination is, indeed, sensitive to the relative local concentrations of the two partners. They are further interpreted to mean that at the time the frequency of interhomologue recombination is determined, homologues are more or less coaligned along their lengths and homologous telomeres tend to be near one another. This finding would be consistent with determination of recombination frequency during or after bouquet formation. On the other hand, telomeres are somewhat clustered in nonmeiotic yeast cells in the absence of any bouquet (148, 162) and this clustering may persist or be present during meiosis prior to bouquet formation.

The event that determines recombination frequency in these studies is not yet established. Lichten and colleagues (M Lichten, T-C Wu & A Goldman, personal communication) favor the view that DSB formation occurs at essentially the same frequency independent of any contact with a homologue (though subtle effects may occur; reviewed in 160), and that the frequency of recombination might be determined by the spatial and temporal limits imposed on the probability that the DSB will interact with a nonsister chromatid, limits imposed by the fixed time available for interaction via the normal interhomologue-biased recombination pathway and by the progressive compartmentalization of the genome by chromosome pairing and condensation. Specific constraints preclude or strongly impede utilization of the sister chromatid in normal circumstances (255, 309). These constraints might eventually be removed or, if the cell

cycle arrests until all DSBs eventually find a partner (186, 305), simply overcome. If these ideas are correct, commitment of a DSB to an interhomologue partner duplex would be the event that usually occurs when homologues are coaligned. Among the interesting implications of the Lichten et al formulation is the fact that the overall probability of a normal interhomologue recombinational interaction could reflect the relative positions of homologues but without requiring any direct dependence of DSB formation on prior contact between homologues.

Assuming that stable partner identification is the frequency-determining event, the coalignment detected in these studies might be achieved before and/or during the bouquet stage. Homologue pairing does not require DSB formation (177, 298), which seems to precede the bouquet stage (see above). Moreover, even during the DSB stage, the earliest steps of partner identification for recombination may well be occurring. Resected DSBs persist for 10–30 min as chemically unaltered entities during this period, and nascent strand invasions of the 3′ tails of DSBs into an intact partner duplex may be ongoing throughout, in preparation for the onset of stable strand exchange (27, 255). It remains to be determined whether pre-DSB homologue pairing, DSB formation, and nascent but stable strand invasion occur as temporally discrete stages or whether they occur in partially overlapping succession, prior to and concomitant with bouquet formation.

Insights from commitment experiments A pioneering study by Olson & Zimmermann (220), who were among the first to be motivated by the idea that recombinational interactions might occur prior to and/or independent of the SC, involved a time course analysis of synchronous meiotic cultures that behave nearly as well as those used in more recent studies (compare 220 and 229 with 40 and 223). SC formation was examined ultrastructurally. Recombination was examined by the only method available at the time, assaying the level of recombination in cells removed from meiotic medium at various times and plated on growth medium suitable for selection of recombinants. This protocol, invented by Sherman & Roman (261) and regularly exploited since by Esposito and colleagues (e.g. 98; see also 309) reveals when meiotic cells become "committed" to undergoing the assayed event. One important finding of the study by Olson & Zimmermann was that commitment to some type of recombinational interaction (irrespective of crossover or noncrossover outcome and signaled by commitment to heteroallelic recombination) occurs well before SC formation, in accord with the timing of DSBs and establishment of interhomologue bias (see above) (255). A second finding was that commitment to crossing over occurs about 2 h later than commitment to heteroallelic recombination, in extension of previous results indicating a temporal separation of the two steps

(98). When these data are analyzed as cumulative curves and compared with the results of more recent studies (223), the second step corresponds essentially to the onset of SC formation, in accord with further progression of recombination to the strand exchange step at this point. Interestingly, the level of crossing over observed in cells that have undergone this return-to-growth protocol is about twofold lower than that observed in wild-type cells (98), precisely the degree of reduction observed in several yeast mutants that specifically lack crossover control (273, 278, reviewed in 245). Thus, when the observations of commitment studies are taken together, the simplest interpretation is that commitment to crossover control occurs at about the onset of SC formation, i.e. the same timing inferred from cytological analysis.

EVIDENCE THAT TELOMERES CAN PROMOTE HOMOLOGUE JUXTAPOSITION INDEPENDENT OF RECOMBINATION Certain haploid strains of *S. cerevisiae* can undergo meiosis. Rockmill & Roeder (244) showed that in such a strain, meiotic prophase progression and subsequent nuclear division are delayed if an extra chromosome is present (i.e. disomic) and that the presence of a delay is independent of initiation of meiotic recombination or SC formation. Moreover, no delay is observed if the extra chromosome is circular or if, with two linear chromosomes, the strain carries a mutation in the abundant telomeric protein Ndj1/Tam1, implicating telomeres in the delay. Furthermore, in a strain that carries a dimeric circular chromosome, rather than comprising two linears, a delay is again observed. These and other findings lead to the interpretation that telomeres (e.g. indirectly via clustering or bouquet formation) promote the juxtaposition of interstitial regions of homologues, which in turn, in this haploid context, induces a prophase delay (244). It seems possible that direct (sub)telomere-specific pairing might also be responsible for the telomeric role.

Microtubule Inhibitors Affect Meiotic Recombination

Colchicine and other drugs that differentially perturb microtubule polymerization have been found almost universally to affect meiotic recombination and other aspects of prophase chromosome metabolism. Despite the strong potential for indirect effects, these observations have provoked considerable speculation regarding the roles of active chromosome movement, telomere attachment, and/or bouquet formation for recombination (reviewed in 30, 108, 176).

HIGH LEVELS OF E0 CHROMOSOMES AND REDUCED CROSSOVER FREQUENCIES Administration of compounds known to affect microtubule assembly to meiotic or premeiotic cells, if given prior to mid-prophase in an appropriate dose, can cause a decrease in the number and/or changes in the distribution of chiasmata as observed at metaphase I. Such effects were first observed in higher

plants (20, 79, 172, 295). These studies have been followed by further plant studies of the wheat/rye group (e.g. 14a, 29, 42, 86, 87, 92, 91, 234, 282, 283), of lily (31, 260, 286), of *Allium* (175), and of *Senecio squalidis* (285). Similar effects have also been observed in rodents (281 and references therein; see also 144). The deficits of chiasmata observed in these experiments likely represent defects in the formation of crossover recombination products per se rather than in other aspects required for bivalent association via chiasmata, e.g. intersister connections. The axial chromosome structure at post-pachytene stages in colchicine-treated cells gives no evidence of any change in intersister associations, in univalents or bivalents. Also, where examined, AE formation can be substantially normal in the presence of colchicine, but complete SCs are rare (e.g. 281) (see below).

All available studies report that colchicine increases the frequency of achiasmate (E0) chromosome pairs as manifested in elevated frequencies of univalents at metaphase I. In addition, however, several studies also report that the increase in achiasmate chromosomes is not accompanied by a correspondingly dramatic change in the number and distribution of chiasmata in chromosomes that have at least one chiasma: frequency and distribution are similar to that observed for all bivalents in the absence of drug, or, at least, the distribution is not as strongly skewed toward low numbers of chiasmata as would be expected if chiasmata were subtracted more or less randomly from the normal distribution. This trend is noted for *Lilium speciosum* (Table 2 of 260); it is apparent in a study of the diploid wheat *Triticum longissimum* and of the autotetraploid *Triticum speltoides*, where dramatic increases in the frequency of achiasmate chromosomes are accompanied by modest changes in the ratio of bivalents that have one or two chiasmata, with the E2 class strongly predominating in both situations (see Tables III and IV of 14a). Thomas & Kaltsikes (283) made a detailed study of a pentaploid *triticale x* wheat hybrid in which it is shown (though not in exactly these terms) that although the number of homologue pairs present as bivalents varies from 28 (in the absence of a colchicine effect) down to 12, the number of chiasmata in the rest of the chromosomes is not very different from what would be expected if they were behaving normally. Interestingly, this study reports that colchicine also produced a few bivalents with a centromere-proximal chiasma, whereas normally chiasmata are mainly terminal. In rye, where normally every bivalent has two chiasmata, the frequency of chiasmata per non-E0 pair (per bivalent) remains at about two even when the total frequency of chiasmata per cell falls substantially, to half the normal level (42, 234). In the diploid *Senecio squalidus*, an increased frequency of chiasmata is seen in cells in which multivalents occur, without any apparent decrease in chiasmata in the rest of the genome (285). And finally, Bennett et al (31) made an extensive analysis of chiasma distribution in *Lillium speciosum* cv. "Rosemeade"

that emphasizes (*a*) that the observed distribution cannot be explained by random subtraction of chiasmata from the distribution observed in untreated cells, (*b*) that shorter chromosomes are more likely to become achiasmate than longer chromosomes, and not just because they start out with fewer chiasmata, (*c*) that among bivalents that retain at least one chiasma, the frequency of chiasmata remains essentially constant, with perhaps a small increase at the strongest colchicine treatments, and (*d*) that despite the constancy of the total frequency of chiasmata per bivalent among non-E0 chromosomes, subtle changes in the pattern of chiasmata are observed with increasing colchicine treatment, arguing against a simple all-or-none phenomenon in which bivalents are either selected to be achiasmate or left unaltered. The possibility is raised that the length of the chromosome arm may be more important than total chromosome length. Bennett et al also suggest that the differential insensitivity to colchicine of an isochromosome compared with normal bivalents in wheat (91) might somehow be related to the differential resistance of longer chromosomes to total chiasma loss. The altered chiasma patterns observed after colchicine treatment may not be qualitatively too different from those observed in a yeast *ndj1/tam1* mutant (55, 63) (see below). Similar effects are observed despite the diverse plant types examined and the diverse treatment regimens utilized.

TIMING OF COLCHICINE SENSITIVITY Another aspect of colchicine action that has been investigated extensively is the stage(s) of meiosis at which the presence of the drug causes disruption of chiasma formation. Such analysis is difficult for several reasons: Because meiocytes are not directly treated by colchicine (entire buds or anthers are submerged or colchicine is injected into the spikes), time is required for uptake of the drug into meiotic cells; despite repeated treatments, the drug may or may not be active indefinitely after administration; the effects of the drug could be cumulative over time, with the result that earlier administrations will have more effect than later ones even though there is a single sensitive stage at the later point (see 31); and finally, colchicine clearly retards (e.g. 283) and in some cases arrests (260) meiotic prophase, and if this effect is not taken into account, the cells that arrive in diakinesis or metaphase I exhibiting effects of colchicine treatment will be inferred to have been at an earlier stage at the time of colchicine treatment than is actually the case. In addition, the drug effect is often estimated from the responses to colchicine of surrounding nonmeiotic cells spindles, which might also be subject to certain variability. Nonetheless, and despite statements in the literature as to strong discrepancies among observed results, the findings are, overall, strikingly similar.

First, colchicine exerts its effects when added after the last premeiotic mitosis. Thus, it is unlikely that the effects of colchicine can be attributed to defective organization of spindle fibers at that last mitosis. Colchicine disruption of

that division can, however, induce polyploidy (e.g. 14a, 31, 86, 234, 286). And in such cases, polyploidization actually increases chiasma frequencies, presumably because it makes available homologous partners in a species whose chromosome pairs were originally largely homeologous (286). Second, the leptotene/zygotene transition appears to be an especially sensitive point of meiosis, and treatment after midzygotene has no effect on eventual chiasma patterns (or SC formation) (see below) in any study. This is true for mice (144; Gibson, cited in 281) and for higher plants (31, 260, 283, 286). Third, several studies emphasize that colchicine exerts its effects only when added earlier than the leptotene/zygotene transition. Organisms may differ with regard to the timing of colchicine sensitivity; it has been argued, for example, that colchicine acts early in organisms that pair their homologues prior to entering meiosis and later in organisms that pair homologues during early prophase (e.g. 14a). Alternatively, it has been argued that there are two colchicine-sensitive aspects of recombination, one involving homologue juxtaposition and the other involving a later step (176). On the other hand, it is also possible that all organisms respond essentially identically, with a single sensitive aspect that occurs at approximately late leptotene or the leptotene/zygotene transition (31), perhaps with some variability in the precise timing relative to the cellular aspects used for staging.

The response of meiotic cells to colchicine treatment is strikingly similar in diverse studies regardless of which stage(s) were inferred to be the sensitive points; this is easiest to understand if there is only one colchicine-sensitive step or aspect. Also, in accord with this possibility, clear evidence is presented for a cumulative effect of colchicine over time; this would imply that perhaps early addition is required only to give an adequate dose at the critical later time (e.g. 260). Additional types of evidence argue for a unified view. In several cases the relevant point is late preleptotene or early leptotene or late premeiosis (20, 79, 172, 260, 295). Moreover, studies on rye and wheat report effects on bouquet formation (42, 282, 283), which is normally diagnostic of a transition at late leptotene/early zygotene, and the first of these determined that late preleptotene or leptotene was the point at which chiasmata were sensitive to colchicine whereas the latter pinpointed the leptotene/zygotene transition. These variations suggest that the differences reported among different organisms or in different studies may be more subtle than they seem from stated conclusions.

DISRUPTION OF SC FORMATION BUT NOT AXIAL ELEMENT FORMATION Cells exposed earlier to colchicine exhibit asynapsis and "pairing gaps" regions in which, by LM, the homologues are near one another but not touching

(144, 172, 259, 260, 281). Ultrastructural analyses revealed at least three SC defects in cells treated before zygotene: uncoupled AEs and SC formation, incomplete SCs, and heterosynapsis. These synaptic perturbations increase with colchicine dose (e.g. for mice, see 281 and references therein; see also 144, 111). Clearly, colchicine has little or no effect on AE and SC formation when lily cells are treated at mid-zygotene (260). In both cases, the authors infer that it is the process of synapsis itself that is aberrant. However, there is an increase in the ratio of AE length to SC length in the cells treated earlier, again implying that AE formation has proceeded without concomitant SC formation. Loidl (175) reports a similar delay in the onset of SC formation in *Allium ursinum*, with a large excess of cells with AEs but no SCs (rare in untreated samples). Interestingly, the vast majority of these cells were blocked with a "*zip1*-like phenotype" (277): aligned AEs with chains of pre-SC "association sites," with the association sites (mainly with homologous AE thickenings at those sites) were separated at distances along the axes (2–5 μm) similar to those normally observed in two other *Allium* species (7). These findings suggest that association and coalignment of homologues is unlikely to be the colchicine-sensitive step and that, instead, nucleation of SC formation per se is affected. Interestingly, in mice, the level of SC aberrencies declined substantially as pachytene progressed. It was proposed that the decline resulted from shedding of defective cells along with Sertoli cells as a consequence of drug treatment (247, 281). Alternatively, SC damage might be repaired at later times, a possibility not unattractive in light of the occurrence of synaptic adjustment at late pachytene in this organism (209). Other studies support the view that absence of chiasmata and nondisjunction in primary mouse spermatocytes leads to their disappearance from the assayable population (13a; see also 216).

All these findings fit well with the notion that the colchicine-sensitive period is at, or immediately before, the leptotene/zygotene transition, i.e. the time of SC initiation. Notably, several yeast recombination mutants also exhibit AE formation but delayed or defective SC formation, and all such mutations affect the DSB to double Holliday junction transition, which occurs essentially at the leptotene/zygotene transition (reviewed in 160, 245). Among these is the mutant *dmc1* (35), and a mouse *dmc1* mutant has essentially the same cytological phenotype (231, 307).

Several studies report that colchicine causes chiasmata to form inappropriately, between homeologous or nonhomologous chromosomes (92, 234 and references therein), though these effects are more subtle than the effects on chiasma patterns among normal bivalents. Colchicine also induces nonhomologous synapsis (confirmed by SC analyses) and consequently multivalent formations in several of the analyzed diploid species (234, 281, 285). In any case,

colchicine treatment does not seem to compromise the discrimination between homologous and homeologous chromosomes. In hexaploid wheat (containing three homeologous diploid genomes), the major effect of drug treatment is on frequency of univalents (and total chiasma frequencies, as discussed above); the proportion of multivalent (trivalent and quadrivalent) chiasmata, i.e. chiasmata between homeologues, is either increased only slightly (92) or decreased to a greater extent than that between homologous pairs (86). The latter finding suggests that homeologous chromosome pairs might actually be more sensitive to the effects of colchicine than homologous chromosome pairs. Also, among several hybrid plants, mild colchicine treatment had a greater effect on those with lower starting chiasma levels, perhaps reflecting stronger effects in organisms with poorer homology (14a). In wheat, although colchicine causes production of pore-less pollen, genetic disruption of the discrimination between homeologues and homologues yields multipore pollen (see 282), again suggestive of two fundamentally different processes. In a hexaploid wheat line also monosomic for a single isochromosome, this latter was relatively insensitive to the effects of colchicine compared with the other chromosomes (91). This finding was interpreted at the time to indicate that colchicine affected the probability of homologue association, with increased spatial proximity of chromosome arms in the isochromosome rendering it insensitive. For another explanation, see below.

BOUQUET DISRUPTION, INTERLOCKING, AND PROPHASE ARREST Two reports suggest that colchicine disrupts bouquet formation (42, 282) or nucleolar fusion, an event normally correlated with bouquet formation (283). Also, induction of chromosome interlocking was observed in hexaploid wheat but does not seem a common effect (see 283). Colchicine treatment can also lead to meiotic prophase arrest. Lily cells exposed early to colchicine arrrest at pachytene stage (with the result that effects on chiasmata could not be characterized), whereas cells exposed somewhat later exhibited lesser or no arrest and proceeded to metaphase I with defective chiasma formation (260, 283, 286). The difference in response could reflect differences in either time of sensitivity or level of colchicine required for the effect (31). In spermatocytes of mice treated with colchicine, a correlation between aneuploidy induction and meiotic arrest was observed with a number of agents, including colchicine and vinblastin (197). These findings are in accord with indications from yeast, and by analogy in mice, that disruption of recombination and/or SC formation can trigger a delay or arrest in prophase progression (35, 160a, 186, 216, 231, 287, 305, 307). In some colchicine studies no arrest is observed (e.g. 234), but in some or all of these cases, the concentration of drug was specifically chosen to permit progression so that effects on chiasmata could be observed.

WHY DOES COLCHICINE AFFECT MEIOTIC RECOMBINATION? Many considerations argue that the primary effect of colchicine is to disrupt homologue pairing and/or synapsis (by either of several mechanisms) (see above) (176). E0 chromosomes would represent homologues that failed to make contact during prophase and defects in SC formation might similarly reflect defects in prior coalignment processes. Contrary to this idea, however, coalignment of homologues appears to occur normally in colchicine-treated *Allium* meiocytes, which exhibit absence of synapsis, at least over substantial portions of the genome (175, 176). Still, colchicine might increase the probability of leftover unpaired chromosomes, e.g. by disrupting bouquet formation (see above). We raise a different possibility: One primary effect of colchicine might be to disrupt meiotic crossover control. If this were the entire story, the abundance of E0 chromosomes would be explained by the loss of the ability to ensure that every pair of homologues gets at least one crossover; other disruptions of the control process would account for the fact that colchicine can disrupt the number and distribution of crossovers modestly, in rather subtle ways. A mixture of both effects is also possible.

In any case, it is important to emphasize the highly critical nature of the DSB to double Holliday junction transition. We have proposed elsewhere that crossover control is imposed at this step (273) (see above). Also, we have pointed out that defects at this stage caused by mutations in components directly involved, the recombination machinery or chromosome structure, might result in a block either to progression of the recombination reaction at the chemical level or, more subtly, on the quality, rather than the number, of the strand transfer products produced. Moreover, if E0 chromosomes arise in part because of a defect in the probability that a DSB can find its partner (see above), prior to imposition of crossover control, even this situation would comprise a block at this critical transition. Furthermore, in yeast and, apparently, in mice, a defect in progression at this stage permits formation of AEs and specifically affects formation of SC and also confers delay or arrest in progression through prophase (3, 35, 210, 231, 307). Thus, if colchicine induced a defect at this stage, the differential defect in SC formation, defects in cell cycle progression, variations in the extent of the crossover defect from subtle to severe, and disruption of crossover control could all be explained.

TARGETS OF COLCHICINE Because of the selective affinity of colchicine for tubulin, MTs have long been suspected to be the main target of these effects. Support for this hypothesis is given by the fact that the colchicine analog lumicolchicine, which does not bind MTs, has no effect on chromosome motion (243, 248) and does not affect meiotic synapsis and/or recombination (see 281). Some considerations suppose that the target of colchicine is cytoplasmic MTs,

on the assumption that there are no intranuclear MTs at prophase. Other considerations suggest that the relevant target of colchicine is nuclear membrane integrity, either as a direct effect on an unknown component or because of effects on membrane-associated cytoplasmic MTs (e.g. 142, 259, 271a).

WHAT ASPECT IS RELEVANT TO RECOMBINATION Many of these considerations suggest that recombination is affected by colchicine because it disrupts chromosome movement, either MT directed via chromosome ends or contacts in peripheral chromatin and/or during bouquet formation (see e.g. 142, 176, 248, 259, 260, 283; see also 48, 147, 288). A second possibility, which we favor for theoretical reasons (see last section), would be that colchicine confers its effects because it causes detachment/release of telomeres from the nuclear membrane, irrespective of movement. Detachment might be anticipated from the nuclear membrane defects often caused by colchicine or anticipatable because of intimate association of MTs with the nuclear envelope. Attachment was claimed normal in cells that have multiple SC formation defects after treatment with Demecolchicine (144), which suggests that at least some associations are intact, but less dramatic or complete effects are certainly possible. Nuclear integrity and cytoplasmic MTs are important for diverse other processes, including various transport processes (65, 198). Disruption of these crucial processes might affect the chromosomes indirectly, e.g. by affecting the concentrations of relevant components or the relative timing of crucial events.

Recombination and Chromosome Ends: Localization, Variations, and Genes

IN PLANT AND ANIMAL CHROMOSOMES *Chiasmata often occur preferentially in subterminal regions* Crossovers/chiasmata/late (recombination) nodules never occur randomly, either along or among meiotic bivalents and they are often distally located (reviewed in 32, 49, 52, 61, 152, 153, 268, 293). Several points must be emphasized.

First, late nodules are not at the chromosome termini exactly but instead are preferentially near the ends, as compared with other regions of the chromosome. In fact, nodules and crossovers are generally absent from heterochromatin in almost all analyzed organisms; for example, they are essentially absent at the ends of tomato SCs, which contain long telomeric repeated DNA sequences (reviewed in 262). Second, chiasmata seldom, if ever, occur uniquely at defined sites, even in cases of extreme localization (e.g. 32, 100); that is, chiasma distribution cannot be specified in the simple terms of unit or very large probabilities at certain sites. Instead, high or unit probabilities of chiasma formation appear to be the properties of regions, arms, or whole bivalents (149, 153). Third, the final distribution is a function of (*a*) the array of total recombinational

interactions, (*b*) where the first (presumably the obligate) crossover occurs within this array, which may or may not be in the region where the density of interactions is highest, and (*c*) the influences of crossover interference. In bivalents that normally only exhibit a single chiasma, the last effect is absent, and localization is still observed (e.g. 102), which implies a role(s) for one or both of the first two factors. Moreover, EN-associated association sites, which may well represent total recombinational interactions, are spaced regularly along the chromosome lengths of two *Allium* species despite differences in chiasma distribution (7), which suggests that much of the final pattern is determined by crossover control mechanisms, at least in this case and in other higher plants. Conversely, where a bivalent normally exhibits two crossovers (or more) (e.g. 150), the situation is more confusing. The fact of interference implies that crossovers must be relatively far apart and, therefore (given the distances over which interference operates), may tend to occur more toward the ends than elsewhere. On the other hand, end-specific effects could influence the occurrence of this distribution, e.g. by ensuring that the first crossover is specifically not at, but instead usually somewhere not too far from, an end. A fourth issue is the relationship between SC and recombination, which is much discussed and is beyond the scope of this review. It is, however, clear that the temporal pattern with which SC forms need not determine the pattern of chiasmata observed at later stages. For example, two *Allium* species with contrasting chiasma distributions, one exhibiting marked centromere-proximal localization and the other exhibiting interstitial and distal (toward the telomeres) chiasmata, exhibit similar patterns of SC initiation and progression (7, 8). Furthermore, in most animals, SC formation frequently starts at telomeres almost exclusively, and even so, chiasmata in these forms are not necessarily preferentially subtelomeric (293, 149). Moreover, although there are strong correlations between SC initiations and crossovers in a number of cases (e.g. 312), the dependency between the two features is the subject of much debate (94, 95, 160, 189, 196; 245, 287). Fifth, several organisms show strongly localized distal chiasmata (examples in 32, 149, 153). Even very extreme situations occur as for example the planarian worm *Mesostoma ehrenbergii*: The three pairs associated by very distally localized chiasmata form three short stretches of SCs with a single or two LNs, confined to a lobe of the nucleus, whereas the two other pairs, seen as univalents at metaphase I, do not form SCs (69).

Isochromosomes Isochromosomes consist of two identical or related arms connected by a centromere. Isochromosomes that are mosaics of homozygous and heterozygous segments show different chiasma distributions depending on which segment is nonmatching. If the proximal (near-centromeric) regions are

heterozygous by virtue of a deletion or of general heterology, chiasma formation is similar to that observed with identical arms, i.e. tending to occur near the telomeric end(s). In contrast, when the heterology is in the terminal regions, exchanges are reduced (185).

Ends and recombination in C. elegans Several genetic phenomena observed in *C. elegans* point to the existence of special behaviors of chromosome ends with respect to recombination (for review, see 4).

First, on the X chromosome, the distribution of exchanges per physical distance is relatively even (22), but at one end of the X has been defined a *cis*-acting site, the integrity of which is required for normal recombination throughout the length of the chromosome (290). Homozygosity for deletions of this site reduces crossing over throughout the chromosome, and no analogous site occurs at the other end of X. Interestingly, mutations in three *trans*-acting genes, *him*-1, *him*-5, and *him*-8, that preferentially increase the frequency of X nondisjunction not only cause an overall reduction in crossover frequency on the X, but they also change the crossover distribution such that crossover levels are normal or higher than normal near the end containing the aforementioned *cis*-acting site, and lower than normal at the other end (43). These observations suggest that an event or process that occurs or intiates near a chromosome end can be communicated along the chromosome to influence the formation of crossovers.

Second, certain types of reciprocal translocations in *C. elegans* are efficient crossover suppressors. In animals heterozygous for such translocation chromosomes, crossing over apparently occurs only on one segment of each half-translocation, i.e. between one particular end (the "HRR" end) and the translocation breakpoint; crossing over distal to the translocation breakpoint is suppressed (reviewed in 300, 310). Similarly, free duplications containing the HRR end of a chromosome can recombine with the homologous region on an intact chromosome whereas other free duplications cannot. These phenomena, which are observed for all chromosomes, also imply some type of asymmetry in the ability of different chromosomal regions to promote crossing over.

These two different sets of observations are probably related, as the *cis*-acting site on the X is at the HRR end of that chromosome. These phenomena have sometimes been attributed to variations in the probability of homologue pairing (and thence recombination). Effects subsequent to pairing, in recombination or in crossover control, are also possible, however. A finding that might support such possibilities is that SC formation is reported to be normal in *him5* and *him8* mutants (119, 120), consistent with normal preSC interhomologue juxtaposition; but the possibility of aberrantly late SC formation cannot be excluded.

Interestingly, cytological studies suggest that only one end of each bivalent appears to be attached to the nuclear envelope, apparently either end (122).

Also there is a special relationship between crossovers, chromosome ends, and homologue disjunction at meiosis I. The position at which the crossover occurs during prophase appears to determine the orientation of the bivalent on the spindle at meiosis I: The end nearest the chiasma is situated at the metaphase plate whereas the other end catches the MTs and leads the way to the pole at anaphase I; the roles are reversed at meiosis II, with the ends that had trailed at meiosis I now capturing microtubules and leading the way to the poles (4–6).

Inhibition of crossing over by chromosome splitting at a centromere In a rye genotype in which chromosome 1R was replaced by two corresponding telocentrics (generated by centric fission) and, in addition, an extra copy of one of the telocentrics, a complex pattern of effects could be explained by an almost complete failure to form chiasmata in the interstitial region spanning the centric discontinuity of the isochromosomes combined with much-more-frequent-than-normal chiasma formation in a terminal segment (235). Failure of homologue association was inferred not to play a role, implying a defect in some other aspect.

Effects of a terminal inversion in mouse For a mouse chromosome that normally has its centromere at one end, a pericentric inversion with one breakpoint 250 kb from that end of the chromosome and the other breakpoing about one third of the way along the chromosome was analyzed for its effects on chiasma number and distribution (13). Normal mice and inversion homozygotes exhibited similar patterns: Two thirds of bivalents showed bichiasmate rings, with one chiasma near each end, whereas one third showed a single chiasma, usually centromere-distal (i.e. closer to the other chromosome end). In the inversion heterozygote, in contrast, the same classes were observed but with one third bichiasmate and two thirds unichiasmate. One interpretation of these data is that in the heterozygote, all bivalents continue to have a crossover at the distal end, but there is a 50% decreased probability of having a crossover at the proximal (rearrangement) end. Interestingly, the inversion moves most of the subterminal microsatellite repeat sequences far away from the end, to the inversion breakpoint. It is suggested that the telomeric repeats per se may be sufficient to confer most, but not all, of any special properties of the ends.

IN *S. CEREVISIAE* *Meiotic recombination at and near telomeres* Crossing over is rare in the immediate vicinity of chromosomal telomeres in yeast. Levels assayed genetically are low (e.g. 78). Also, there are no detectable DSBs in the terminal 15–30 kb of any chromosome (average size ~1000 kb) (26, 180, 308) (Figure 11), including the telomeric repeat sequences.

The structure of yeast telomeres includes not only the terminal 300 ± 75 bp of TG1-3 repeats but other sequences, several of which have known

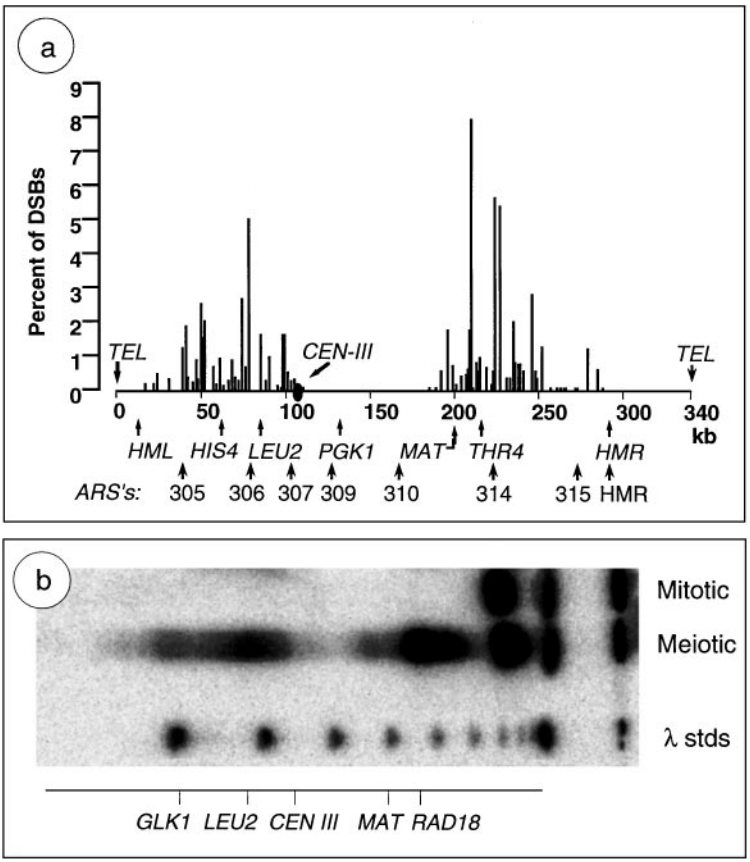


Figure 11 Double-strand breaks (DSBs) distribution along chromosome III of *Saccharomyces cerevisiae*. (*Top*) Molecular mapping (26); (*bottom*) visualization of DSBs along an entire yeast chromosome by pulse field gel separation, Southern blotting, and visualization with a probe to *CHA1* sequences (*left end*). (T-C Wu, M Lichten, personal communication; see also 308.)

determinants and/or protein binding sites (233). The latter include the following: (*a*) a 450 bp core X element, near the terminal TG1-3 or separated from the terminal TG1-3 by one or more tandem Y′ elements; (*b*) usually, one of several small subtelomeric repeats (STR-D, -C, -B, or -A) located between the X and terminal TG1-3 or adjacent Y′; and (*c*) the Y′ elements, which are highly conserved but variably located among ends in different strains and usually separated from the X and STRs by a short tract of TG1-3. Centromere

proximal to the X element are usually larger but less widely dispersed repeats, also variably shared by different chromosome ends in different strains. Many of the multigene families found in subtelomeric regions are in this region, however some of the amplifications seen in brewing strains are between the X and Y′. The general structure of yeast chromosome ends is remarkably like that of humans (101) and in fact not dissimilar to all linear chromosomes (232).

DSB and/or recombinational suppression near chromosome ends is not eliminated by deletion of an X element or when various unique sequences from other regions of the genome are inserted (E Louis, personal communication), in contrast to the fact that ectopic insertions elsewhere often create meiosis-specific DSB hot spots (e.g. 48a). Mutations in genes that affect telomere silencing, e.g. *SIR1-4*, also have no effect (E Louis, A Nicolas, personal communications).

Sequences located near a chromosome end, i.e. distal to the X element, exhibit other special recombinational properties (141, 233; E Louis, personal communication). While recombination between homologues within this region is low (above), a sequence in such a region recombines actively with an homologous sequence located near the end of a nonhomologous chromosome, at higher levels with ends sharing greater overall homology. Even so, a sequence near an end will not recombine with an homologous sequence in a nonterminal location. Thus: a sequence located near a chromosome end is precluded from recombining if an homologous sequence is located allelically on the homolog, or at any non-terminal site, but not if it is located near the end of a nonhomologous chromosome. Such effects occur for both microheterogeneous elements native to chromosome ends and tester sequences inserted artificially.

These behaviors occur in both mitotic and meiotic cells. The mitotic effects are known thus far to be abrogated by mutations affecting KU70 and KU80 proteins, the checkpoint control genes *RAD17* and *RAD24*, the mismatch repair gene *PMS1*, and the only chromodomain protein in budding yeast, *CHD1*. Of these, only *rad17* and *rad24* mutations abrogate the meiotic effects, which implies specialized control during meiosis. These phenomena likely are related to differential control of recombination in rDNA versus other interstitial regions during meiosis (e.g. 103) and of axis-associated meiotic interhomologue recombination, as compared with intrachromosomal meiotic recombination (255, 191).

Interestingly, the *MRE11*/*RAD50*/*XRS2* genes are required for formation and terminal processing of meiotic DSBs as well as for recombinational repair and nonhomologous end joining in mitotic cells (e.g. 3, 205, 217) and possibly pre-DSB homologue pairing (298). And this complex is also required in mitotic cells for normal telomere length maintenance, acting in the same genetic pathway as telomerase and in a different pathway from the KU proteins (215, 159, 41).

Given a role for Rad50/Mre11/Xrs2 in intersister interactions (2, 205), the idea of a structural role in telomere replication is attractive (V Lundblad, personal communication).

Genes that may link recombination with telomeres or microtubules The *NDJ1*/*TAM1* gene encodes a meiosis-specific protein. Immunofluorescent antibodies against Ndj1/Tam1 protein prominently stain telomeres in meiotic prophase cells, raising the possibility of an important role for this protein in telomere function (55, 63). Indeed, an *ndj1* mutant exhibits atypical telomere organization at mid-prophase, as revealed by immunostaining with anti-Rap1 antibodies: In wild-type pachytene cells, 32 foci are observed, as expected if, at each of the two bivalent ends, all four chromatids are closely associated; in the mutant, approximately twice as many foci are observed, which suggests, for example, loss of intimate association between homologues at the chromosome ends. Also, an *ndj1* mutant is defective for distributive segregation of nonhomologous linear artificial chromosomes but not for the corresponding circular ones, consistent with a role at telomeres.

No immunolocalization of Ndj1/Tam1 protein along the lengths of chromosomes has been detected, though small interstitial amounts cannot be excluded. Also, two *ndj1*/*tam1* mutant phenotypes might (or might not) indicate a role for Ndj1/Tam1 in interstitial regions. (*a*) AE formation is delayed (63); telomeric associations could play a crucial nucleating role, or alternatively, defects in intersister interactions along chromosomes or indirect effects via cell cycle regulatory processes could be responsible. (*b*) The mutant exhibits prominent defects in chromosome segregation, including premature segregation of sister chromatids at and errors at metaphase I (55, 63). Such effects could reflect dissolution of centric intersister connections prior to metaphase II because of a direct defect in cohesion; alternatively, telomere behavior could affect segregation indirectly, e.g. because cell cycle signals for dissolution of centric connections occur too early, relative to bipolar orientation of chromosomes at metaphase II (see 55, 63).

Ndj1/Tam1 does not play a major role in ensuring efficient interhomologue recombination: The frequency of commitment to gene conversion and of aberrant segregation and crossing over in four spore-viable tetrads is normal, or nearly so, though deviations of ±30–50% below or above the wild-type values are observed. The protein might, however, play a role in crossover control. One study reported a defect in crossover interference as inferred from two- and three-factor crosses as well as an increase in the frequency of chromosomes that failed to exhibit even one crossover along their length and, thus, disjoined (55). In another study, however, crossover interference was essentially normal, with minor increases or decreases as compared with wild type

(63). Similar results were obtained for all other parameters, so overall differences in physiology may not explain the difference. Perhaps the difference lies in the extent of end-specific effects on recombination (ME Dresser, personal communication). The study that detected interference analyzed a short chromosome, where all regions might be effectively under influence of an end; the second study analyzed internal regions of a long chromosome.

Three yeast genes might possibly be involved in microtubule-directed chromosome movement. Mutations in *VPS1*/*SPO15*, *KAR3*, and *SEP1* (aka *KEM1*, *XRN1*, *RAR5*, and *DST2*/*STP-*β) all confer late prophase arrest and various phenotypes, which suggests a defect in prophase chromosome metabolism (16, 23, 285a, 306). However, although *VPS1*/*SPO15* encodes a dynamin-related GTPase that associates with MTs in vitro (215a, 306), MT association may have no in vivo significance for any member of the dynamin family (287a); by contrast, Vps1/Spo15 is involved directly in vacuolar protein sorting which, in vitro, is independent of microtubules (96a). In addition, the *KAR3* gene of yeast encodes a motor protein that moves toward the minus ends of microtubules in vitro and (*a*) is required for nuclear fusion during karyogamy, (*b*) plays a role in spindle development in mitotic cells, and (*c*) is required for meiosis (for review, see 23). In addition to prophase defects, however, another study found that the master meiotic regulatory gene *IME1* was not fully induced (P Meluh, M Rose, personal communication), warning of indirect effects. Also, the *SEP1* gene encodes a large multifunctional nuclease, active on both DNA and RNA, which appears to play direct roles in RNA turnover and the microtubular cytoskeleton. Sep1 protein was initially identified in yeast by five unrelated approaches, genetic and biochemical, but is evolutionarily conserved (for summary, see 23a, 24). Involvement with microtubules was indicated by the identification of this gene as a mutation that enhances the defect of a mutant defective in the MT-driven process of karyogamy (157) and confirmed in further studies (142a, 143). A role in RNA turnover, via the exonuclease activity, has similarly been revealed by several types of studies (reviewed in 24). These two aspects may be related, given the recent identification of proteins that bind RNA and track along MTs and the quantitative association of mRNAs with microtubules.

Another interesting property of Sep1 protein is its ability to bind and hydrolyze G4 tetraplex (or G-quartet) structures, proposed to occur with special abundance at telomeres (reviewed in 301). And G4 structures, with help from Sep1, have been proposed to mediate pairing of the four meiotic chromatids during meiosis (173, 174, 257). It has been proposed more generally that Sep1 is a microtubule-nucleic acid interface protein, occurring at the interface between cytoplasmic microtubules and chromosomal telomeres, and that this role could be especially important in meiotic cells (24). Mutants specifically defective in the Mg^{2+}-coordinating residues of the exonuclease active site, but still active

for MT binding, mimic an *sep1* null mutation for mitotic phenotypes (which implies a crucial role of RNA turnover in these defects) but are significantly less defective than the null for meiotic defects. This implies that activities of Sep1 protein other than RNA turnover are important for these defects and is consistent with the possibility of a direct role for the MT binding function during, and specific to, meiosis (W-D Heyer, personal communication).

IN *S. POMBE* For fission yeast, it has been proposed that nuclear movement facilitates meiotic chromosome pairing, which in turn promotes recombination (53, 163, 164, 276). In support of this idea, disruption of the unique cytoplasmic dynein gene disrupts nuclear movement and causes a 5- to 10-fold reduction in meiotic recombination frequency, and data suggest that homologous centromere-linked loci are not paired in the dynein disruption mutant (Y Hiraoka, personal communication).

Mutations that disrupt SPB and/or telomere organization also confer defects in meiotic prophase chromosome motion, as led by the telomeres (see above), plus severalfold reductions in meiotic recombination. (1) The *kms1*$^+$ gene, isolated as impaired in karyogamy, is important during meiosis for normally elongated nuclear shape, normal levels of meiotic recombination, clustering of telomeres, and normal localization of the SPB component Sad1 (263). In the mutant, multiple large foci are observed for both telomere sequences and Sad1 protein, possibly reflecting clustering. Dynamic nuclear movement is much less smooth than normal and is seemingly less uniform in pattern from one nucleus to another. (2) Taz1 is a telomere binding protein (64), and corresponding mutations cause lengthening of telomeric repeats in nonmeiotic cells (214). Two studies report that *taz1* mutations reduce clustering of telomeres with one another and reduce association of telomeres with the SPB, though the SPB itself appears intact (64, 214). Interestingly, a *taz1* defect in haploid cells prior to karyogamy cannot be complemented by *taz1*$^+$ after karyogamy, consistent with the establishment of SPB/telomere contacts prior to conjugation (53). During the horsetail stage, the morphology of the nucleus is aberrant, and attachment of the SPB to the nucleoplasm seems unusually tenuous (64); also, in a severely defective mutant, the bulk of the nucleus remains stationary, with only a thin extrusion of nucleoplasm moving back and forth (214). The fact that mutations in dynein and *kms1* or *taz1* exhibit similar phenotypes is consistent with the possibility that they act in a common pathway with regard to recombination.

These findings are all consistent with the idea that SPB/telomere interactions are required for chromosome movement, which in turn is required for fully efficient juxtaposition of homologues, which in turn is required for maximal levels of interhomologue recombination. Possible roles for such movement have been considered above. Increased juxtaposition of homologous sequences is

a favored view, but if so, why should such dramatic motions be important for *S. pombe* but, apparently, not for *S. cerevisiae*? Perhaps budding yeast chromosomes are more flexible or more loosely organized (a hint could be the fact that ectopic recombination is much rarer in fission yeast than budding yeast) (291). Or perhaps it is the presence of an elongated nuclear shape that is required for homologue coalignment rather than the attendant movement. A more speculative possibility is that efficient initiation of recombination requires normal development of axial chromosome structure, which in turn requires "getting out the kinks." Finally, disruption of the SBP/telomere complex might disrupt dynein-mediated cytoplasmic transport processes, which in turn are required for normal recombination, or nuclear membrane architecture may be abnormal, even in the dynein mutant, with ensuing indirect effects. It can also be noted that meiotic recombination in *S. pombe* is atypical in that there is no crossover interference (164).

A Crossover Control Model that Predicts Variations in Crossover Number and Position According to the Status of Chromosome End(s)

A model has been proposed for crossover control that involves the imposition of tension along the axes of meiotic chromosomes (160, 273; N Kleckner, manuscript in preparation). The chromosomes are considered analogous to an elastic beam coated with a thin brittle film containing a number of flaws. Differential compaction of the film relative to the beam creates tension at the beam/film interface, which is felt as stress at the sites of the flaws. If tension becomes high enough, the most sensitive flaw will go critical, developing into a crack across the beam. Tension/stress will be alleviated in the immediate vicinity of the crack, with the level of alleviation decaying with distance away from the initiating site. If the tension (or sensitivity of flaws to that tension) continues to increase, additional flaws go critical, but with a tendency not to occur near one another, i.e. not within the effective stress relief distance. Eventually, an even (not random) distribution of flaws will result. If the chromosomes are the beam/film ensemble and undifferentiated recombinational interactions are the flaws, and if cracks correspond to crossovers whereas flaws that never go critical correspond to noncrossovers, the two basic aspects of crossover control are explained. Parameters are set to ensure (*a*) that one flaw goes critical on every beam and (*b*) a biologically relevant stress relief distance. In real chromosomes, tension would be imposed, e.g. by compaction of supra-axial structural components along the lengths of the chromosomes against resistance from the underlying axis or core, stress would be sensed directly within the recombination complex, and alleviation of stress would involve release of the connection between the core and overlying structural meshwork. Several

changes that could correspond to imposition of stress have been reported at what could be the relevant time of meiosis, including but not limited to the following: a specific change in chromatin loop status in yeast (222); an interesting, programmed, transient tendency for splitting of sisters in many organisms (207; for an especially interesting study, see 90); a corresponding tendency for enhanced sister separation at the leptotene/zygotene transition of maize (74); and other variations in bulk chromosome status (252, 253). Also, the yeast chromosome structure protein Hop1, which is required for early chromosome morphogenesis and meiotic DSB formation, changes chromosome localization at about this time (265a).

In this model, the ends of the chromosomes can have special status for either of two reasons. First, they could have a specialized chromatin structure (e.g. subtelomerically) that permits either more (or less) stress or makes recombinational interactions more (or less) sensitive to stress in those locations. Second, most uniquely, the end status must be specified: ends either are, or are not, "clamped," i.e. connected to something (e.g. the nuclear envelope). And an unclamped end will be the equivalent of a preexisting crossover, thus tending to exclude crossovers (even the first obligatory crossover) from its vicinity. Thus, for example, if an end that is normally clamped becomes unclamped, crossovers will be less frequent in regions near that end (and, correspondingly, redistributed to other positions, with perturbations all along the chromosome). Furthermore, if an end is clamped, crossovers that occur after the first obligatory crossover will be more frequent in the near-terminal region than in an equivalent interstitial region because relief of stress can not emanate into that region from beyond the end. Such effects can, in principle, explain many of the observations presented above regarding the role of telomere status in meiotic crossing over. Perhaps colchicine and/or *ndj1/tam1* mutations exert their effects on crossover control by eliminating clamping (nuclear envelope attachment). Perhaps the effects of centromere splitting reflect the fact that each resultant new chromosome has one unnatural, and thus unclamped, chromosome end. Perhaps a fully homologous isochromosome is differentially insensitive to colchicine because its "centromere end" is already unclamped in the absence of durg. Perhaps the fact that heterology between arms of an isochromosome affects crossover patterns only when heterology is at the normal "noncentromere" end reflects the fact that loss of clamping can occur only at that end. Perhaps certain properties of small chromosomes, e.g. a higher basic level of crossing over and increased crossovers upon shortening (e.g. 153a) and/or possible differential sensitivity to an *ndj1/tam1* mutation (above) reflects, at least in part, the fact that a greater proportion of the chromosome is now under the influence of clamped ends. Perhaps *C. elegans* translocation behavior is explained by existence or differential effects on end attachment in the translocations and/or

by disrupted transmission of stress by the translocation breakpoint; and perhaps the effects of *him* mutations on the distribution of crossovers relects a change in chromosome structure so as to reveal underlying features that give end-proximal chiasmata as the normal condition in other organisms.

There is no explicit role for chromosome movement in this model. The model does, however, require smooth, regular development of axial chromosome structure. Perhaps some back-and-forth motion of chromosomes (linear or rotary, gentle or dramatic) would be useful in ensuring that the chromosome axes are structurally uniform, i.e. "to get the kinks out." If so, at least gentle movement could be important not only for imposition of stress, but—given appropriate coupling—for progression of recombination through the corresponding transition, thus explaining the need for motion even in *S. pombe*, where crossover interference is absent. There is also no explicit role for the bouquet in this model, but a general possibility is suggested below.

CONCLUSION

Chromosome ends could play a role in meiosis because of movement into and out of the bouquet, existence of the bouquet, active chromosome movement directed by chromosome ends via their telomeric attachments, and/or effects of attachment irrespective of chromosome movement. Finally, however, in contrast to the apparent complexity of underlying events, the bouquet stage remains a remarkable landmark. It represents the single unique point of meiosis in which all chromosomes, irrespective of their overall organization in internal regions, are spatially equivalent, especially with regard to the configuration of the ends. Had meiotic cells simply kept the Rabl, with chromosomes hanging from their centromeres, a general disorganization of the ends would persist because of their different latitudes and the potential for different positions within the volume of the nucleus. And the necessary homologue pairing during meiosis provides further disorder. In the bouquet, in contrast, all ends are in a uniform configuration in a single two-dimensional space and in intimate contact with the space outside the nucleus. If some particular signal must be sent to the chromosomes via the ends, for movement, for transmission of stress, or for any other purpose, the bouquet condition provides a unique opportunity for a coordinated response.

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in the several topics. Thus, we often made the choice to cite what seemed to be the most illustrative example for what we wished to say. We tried also to use examples of all possible techniques used to study meiosis, and all papers using the same technique could not be cited. We hope that students, teachers, or colleagues who wish to learn more about meiosis will benefit from these difficult but necessary choices. We know, however, that inevitably, despite our best efforts, one or another author will not consider that he is cited for what he thinks is the most important part of his work. Several reviews have been written on meiosis and all cited papers have lists of references: We invite the reader to complete his knowledge from those lists and reviews. We are also especially grateful to Allan Campbell, who, as friend, mentor, and Editor, has made possible both the initiation and the completion of this endeavor. Also we thank Jim Henle, without whose tireless supporting contributions we could have never finished. Finally, we thank the institutions that have supported our individual research programs in meiosis. DZ is grateful for support from the Centre National de la Recherche Scientifique (URA 1354) and from the European Economic Community (contract CHRX-CT94-0511). NK is grateful both to the National Science Foundation, which was uniquely willing to support her research on meiosis in its earliest stages, and to the National Institutes of Health, which has generously supported recent and ongoing work in this area (GM44794 and GM25326).

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