sign and thus average out to yield more modest variations for the Northern Hemisphere on the whole (*9*, *10*). In recent decades, Europe has warmed faster than the Northern Hemisphere on the whole, whereas certain regions in the North Atlantic have actually cooled in the face of widespread warming. This is a result of a combination of regional temperature overprints by the North Atlantic Oscillation (NAO) and related, but distinct, patterns of multidecadal variability associated with the thermohaline circulation of the North Atlantic (*16*, *17*).

It is quite reasonable to assume that similar factors were associated with the pronounced temperature changes in Europe in past centuries that accompanied more modest hemispheric-wide temperature changes. Keigwin and Pickart (*18*) have shown evidence that a heterogeneous temperature pattern in the North Atlantic region consistent with the NAO coincided with the European Medieval Warm Period and Little Ice Age. There is evidence that the aforementioned multidecadal variations in the North Atlantic can couple to variations in solar radiative output that occur on similar time scales (*19*).

Could a similar mode of North Atlantic variability resonate with solar radiative variations at millennial time scales, imprinting a regional pattern of enhanced anomalies on top of the more modest hemispheric-scale warming that Crowley's study attributes in part to solar forcing at these time scales? Only further, more detailed modeling studies and expanded networks of paleoclimate indicators will further elucidate the spatial and temporal patterns of climate change in past centuries.

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PERSPECTIVES: MOLECULAR BIOLOGY

The Mad Ways of Meiosis

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Many organisms, including ourselves, are diploid, that is, they have paired homologous chromosomes (1, 2, 3, and so on) and two sex chromosomes (XX in females and XY in males). Meiosis is the cellular process by which diploid reproductive cells shed one whole set of chromosomes before they differentiate into haploid gametes (sperm or egg). This remarkable process involves two steps, each accompanied by a reduction in chromosome number. First, all the chromosomes replicate to form joined pairs of chromatids; then, homologous chromatid pairs bind (synapse) to each other (see the figure). The homologs separate and are pulled to opposite spindle poles and the cell divides into two daughters (meiosis I). Immediately thereafter (without an intervening interphase) a second spindle is assembled in each daughter cell, and the sister chromatids of each homolog are segregated equally to opposite spindle poles (meiosis II).

A low incidence of unequal chromosome segregation during meiosis seems to be no big deal—right? Wrong. For humans the gain or loss of just a single chromosome during meiosis in either egg or sperm can have devastating consequences. On page 300 of this issue, Shonn *et al.* (*1*) suggest a possible cause of chromosome missegregation during meiosis and propose that the fidelity of chromosome distribution depends on the signaling protein Mad2.

About 20% of all conceptions have major chromosomal abnormalities caused by missegregation of chromosomes during meiosis (*2*). Most fetuses with autosomal trisomy (three copies of a chromosome) and all of those with autosomal monosomy (one copy of a chromosome) are spontaneously aborted. Fetuses with autosomal trisomy of chromosomes 21 (Down syndrome), 13 (Patau syndrome), or 18 (Edwards syndrome) survive until birth but have severe physical and mental abnormalities. Trisomies of the sex chromosomes include XXY (Klinefelter syndrome), which results in mental retardation and sterility, and XYY, which may be associated with a predisposition toward antisocial behavior.

At the onset of meiosis I or II, a specialized complex of proteins on each chromatid, called the kinetochore, captures microtubules coming from one of the two spindle poles (see the figure). For chromosome segregation to be equal, each homolog in meiosis I and each sister chromatid in meiosis II must become attached to microtubules coming from opposite spindle poles. Sister kinetochores, however, do not capture microtubules simultaneously; as a consequence, the chromosome pairs begin to move toward the pole belonging to whichever microtubules they attach to first. The problem is that the amount of time required for the unattached kinetochores to capture microtubules emanating from the other (now distant) pole is highly variable. This difficulty is compounded by the small number of microtubules that extend far enough to reach the unattached kinetochores. If the cell initiates anaphase and starts to segregate chromosomes before all the homolog pairs have established connections with both spindle poles, some gametes will inherit two copies of a missegregated chromosome, and others none (see the figure). Two copies of any chromosome in one of the gametes causes trisomy in the embryo; no copy of any chromosome (except X or Y) gives rise to monosomy, an embryonic lethal abnormality. The loss of the X or Y chromosome in sperm produces the XO genotype (Turner syndrome).

Somatic cells in mitosis (normal cell division) ensure the correct attachment of daughter chromosomes to opposite spindle poles by a molecular safeguard called the spindle checkpoint. This checkpoint detects the presence of even a single unattached kinetochore and arrests the progress of mitosis until the unattached kinetochore captures microtubules from the distant spindle pole. Mutations that compromise the spindle checkpoint contribute to chromosome instability, a hallmark of many human cancers (*3*). Although the activity of this checkpoint in meiosis has been documented in insect spermatocytes (*4*), most analyses have been conducted in mitotic cells, with scant attention devoted to the checkpoint's importance in meiosis.

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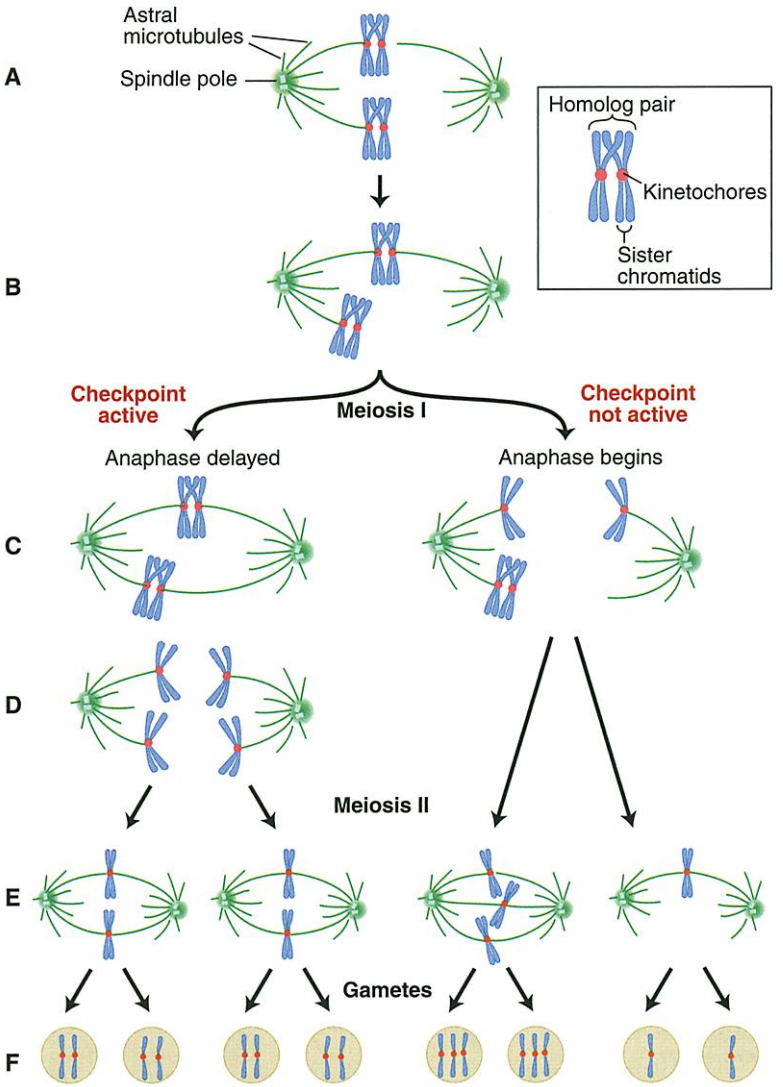
Now Shonn *et al.* (*1*) have used a number of clever manipulations in budding yeast, applying the power of genetics to address this issue. Their approach was to tag the kinetochore regions of both homologs of a given chromosome with a fluorescent reporter construct. They then determined whether the four tagged chromatids were equally distributed during meiosis to all four gametes (spores) in the presence or absence of MAD2, an essential component of the spindle checkpoint in mitotic cells. Nondisjunction during meiosis I (in which any homolog pair ends up at the same spindle pole) yields two spores with no tagged chromosomes and a pair of spores with two tagged chromosomes. The authors found that inactivation of the spindle checkpoint by mutation of MAD2 led to a large increase in the rate of chromosome missegregation during meiosis I but did not significantly increase the error rate for meiosis II over that for wild-type cells. The incidence of chromosome missegregation increased in a roughly linear fashion as the chromosome length increased, reaching 19% for the longest chromosome. Even though the rate of missegregation for the shorter chromosomes was lower, the total error rate for the whole chromosome complement was higher in cells without a functional spindle checkpoint compared with wild-type cells.



Split decisions. Segregation and missegregation of chromosome pairs in meiosis I and II. (**A**) As the nuclear envelope breaks down, microtubules grow toward the replicated chromosomes (homolog pairs) and some are captured by the kinetochores of the homologs. (**B**) Because not all kinetochores capture microtubules at the same time, some homologs may start to move toward the same spindle pole. (**Left**) (**C**) The spindle checkpoint delays anaphase onset until the unattached kinetochores capture microtubules from the opposite pole and start to move toward it. (**D**) Then anaphase of meiosis I proceeds normally with equal segregation of homolog pairs. (**E**) During metaphase of meiosis II, both spindle poles have the same number of chromosomes; (**F**) after meiosis II anaphase, all four gametes inherit the correct chromosome complement. (**Right**) (**C**) If the checkpoint pathway is compromised, meiosis I anaphase begins with a homolog pair attached to only one spindle pole. (**E**) During the first anaphase, one spindle pole has three chromatid pairs, and the other has only one. (**F**) After meiosis II anaphase, two gametes inherit three chromosomes and two inherit only one chromosome. (In mammals, the formation of four viable gametes in meiosis would correspond to spermatogenesis; during oogenesis only one meiotic product, the egg, forms; the others are polar bodies.)

One possible explanation for why absence of the spindle checkpoint affects meiosis I and II differently is that the chromosomes are held together differently during the two meiotic divisions. In meiosis II, the sister chromatids are connected directly to eachother at their kinetochore regions, which may prevent both kinetochores from attaching to microtubules from the same pole. Due to recombination, pairs of homologous chromosomes in meiosis I are held together by connections along their arms at specific points. Thus, in meiosis I, the longer the chromosome the greater is the potential distance from the centromere (the constriction point of the chromosome that contains the kinetochore) to a recombination site; this creates a more flexible linkage between the kinetochores of the two homologs. This flexibility may make the kinetochores of the two homologs functionally more independent, thereby increasing the incidence at which both chromatid pairs attach to microtubules from (and move toward) the same spindle pole. Consistent with this view, Shonn and colleagues show that experimentally delaying the onset of anaphase (the last step before the cell divides into two daughter cells) rescues chromosome segregation defects in the checkpoint-defective mutants by allowing more time for the cells to rectify inappropriate chromosome attachments.

Looking forward, it will be important to determine the extent to which the spindle checkpoint is required for equal segregation of chromosomes during meiosis in more complex organisms. Recent studies suggest that the spindle checkpoint is important in meiosis of cells from worm (*5*) and fly (*6*). It will be intriguing to see whether meiosis I in humans is more sensitive to checkpoint defects than meiosis II or mitosis. If so, then weak loss-of-function mutations in any of the components of the spindle checkpoint pathway could allow normal development to adulthood but cause a high incidence of chromosome missegregation during meiosis I. This could contribute to the difficulty that many couples face in achieving full-term pregnancies owing to a high rate of fetal trisomy or monosomy resulting in repeated spontaneous miscarriage.

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