11

Meiotic Abnormalities: Abnormal Numbers of Chromosomes

Aneuploidy is the loss or gain of individual chromosomes. It can be the result of nondisjunction in a premeiotic mitotic division in the germline of either parent, a first or second meiotic division in either parent, or an early embryonic mitotic (*postzygotic*) division in the affected individual. Nondisjunction refers to any process that causes two homologous chromosomes to go to the same pole instead of segregating to opposite poles. Some meiotic aberrations leading to nondisjunction are described in Table 11.1 and illustrated in Fig. 11.1. When homologous chromosomes fail to pair or fail to form chiasmata the homologues fall apart and appear as univalents in diplotene. Univalents may drift at random to the two poles in the first division and divide regularly in the second. Alternatively, they may divide mitotically in anaphase I and in anaphase II drift at random to opposite poles or fail to go to either pole, rarely, one may misdivide at the centromere, just as univalents might in the first meiotic division. Only a small

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Table 11.1. Principal Meiotic Events and Outcomes of Their Failures

Stage	Meiotic events	Results of unsuccessful completion of meiotic events
Leptotene	Chromosomes become visible; lateral elements begin to form	Germ cell degeneration; sometimes nondisjunction
Zygotene	Chromosomes form bouquet; each chromosome pairs with its lateral element; homologous lateral elements unite into a synaptonemal complex, which completes the pairing	Germ cell degeneration; sometimes nondisjunction
Pachytene, early	Recombination nodules attach to the central elements	No crossing over; chromosomes remain univalent
Pachytene, late	During crossing over, recombination nodules change into bars	Because of lack of chiasmata, bivalents fall into univalents
Diplotene	Homologues repel each other until they are held together only at the chiasmata	More univalents visible than in earlier stages
Metaphase I, Anaphase I, Metaphase II, Anaphase II	Orderly segregation of chromosomes is prerequisite for regular gametogenesis	Univalents may undergo nondisjunction, loss, or misdivision; spindle abnormalities interfere with chromosome segregation

segment of the XY bivalent forms a synaptonemal complex in which crossing over takes place (Fig. 17.2). Thus, the X and Y remain as univalents much more often than even the smallest autosome pair. Frequencies of univalents vary among different individuals, but the mean frequency of unpaired sex chromosomes in the male is about 11 per cent (Laurie and Hultén, 1985). Multiple aneuploidy of one or several chromosomes is very uncommon, except for the sex chromosomes. Polyploidy (triploidy or tetraploidy) is the gain of whole sets of chromosomes.

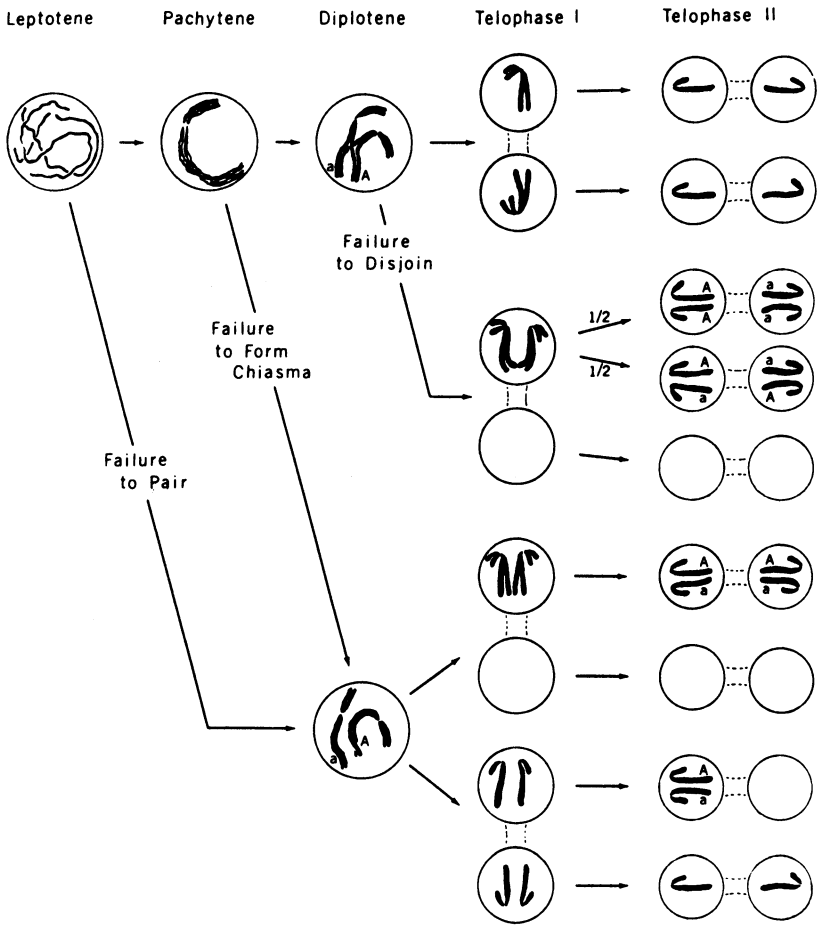

Figure 11.1. Diagram of the processes resulting in meiotic nondisjunction (see text) (Patau, 1963).

Incidence of Nondisjunction in Meiosis and Gametes

Direct analysis of male and female meiosis is difficult and limited by the availability of material. All stages of male meiosis can be studied in the adult testis, but this provides only a small amount of information about the incidence of nondisjunction in a particular individual. Corresponding information in the female is much more limited. The early prophase stages in the

female are observable only in the fifth month of fetal life. The later stages of female meiosis I and meiosis II occur during the reproductive years of the adult, but usually only one ovum is released in each menstrual cycle. However, hormonal stimulation can induce superovulation of a small cohort of ova. This technique is widely used in clinics that carry out in vitro fertilization as a means of overcoming infertility. Superovulated ova in excess of those needed for fertilization or that have remained unfertilized by added sperm may be used to analyze the chromosomes of both the metaphase II oocyte and its corresponding polar body.

Angell (1995) studied oocytes removed by aspiration from the ovaries of 26- to 37-year-old women and matured in vitro. Germinal vesicle breakdown took about 12 hours and was followed by a 10- to 12-hour diakinesis. Chiasmata could not be well visualized at this stage, but their distribution was clearly different from that seen in males. Only 22 analyzable metaphase I configurations were seen, but two of these each contained a pair of univalent chromosomes and two each contained two pairs of univalents. In contrast, Hultén (1974) saw no univalents in 2168 metaphase I configurations in males, including 500 from an 86-year-old man. Clearly, female meiosis is much more error-prone than male meiosis, and increasingly so at advancing maternal ages.

The haploid products of meiosis must successfully complete gametogenesis if they are to become sperm or ova, and this might be less likely to occur if a particular chromosome is missing or present in excess, as in some nullisomics or disomics. Examination of meiosis is essential for working out the mechanisms involved in nondisjunction, but it cannot explain the widely different frequencies of the different trisomies or other numerical abnormalities in abortuses or liveborns.

Two methods have been developed to analyze the chromosome content of male gametes. The first involves fusion of sperm with hamster oocytes from which the zona pellucida has been removed enzymatically and observation of the first cleavage division several hours later, when the male and female metaphase plates are distinguishable and every human chromosome identifiable by banding (Rudak et al., 1978). Surprisingly high frequencies of chromosome abnormalities are seen using this technique, with considerable variation among studies. In a comprehensive review, Guttenbach et al. (1997) summarized data on 18,000 sperm karyotypes from normal men. Hyperhaploidy (usually disomy) occurred, on average, in 1.7% and hypohaploidy (usually monosomy) in 3.3% of the sperm. The chromosomes most frequently present in an extra copy were 21, X or Y, 16, 9, and 1. Structural abnormalities were seen in 6–7% of sperm.

This may be relevant to the observation that 84% of de novo translocations have a paternal origin (Olson and Magenis, 1988).

The second method is to examine chromosomes in chemically decondensed sperm using molecular techniques, such as multicolor FISH with two to five chromosome-specific α-satellite probes. This method has the advantage that very large numbers of sperm from an individual can be scored quickly. Consistent results can be obtained from person to person if the same technique of sperm decondensation is used. Again, the frequency of disomic sperm is quite high. Guttenbach et al. (1997) examined chromosomes 1, 7, 10, 17, X, and Y in both fertile and infertile men; 43 of 45 infertile men showed no differences from the fertile men. The frequencies of disomic sperm ranged from 0.1% for the Y to 0.14% for chromosome 10 and the X. The frequency of diploid sperm was 0.1%. Two of the 45 infertile men had 7- and 23-fold higher frequencies of diploid sperm: 0.35 and 1.6% vs. 0.06% in the other 43.

Guttenbach et al. (1997) reviewed results of more than 40 studies, involving every chromosome. In general, no chromosome showed a higher incidence of hyperhaploidy than any other chromosome. Pellestor et al. (1996) used primed in situ labeling (PRINS; Chapter 8) to determine the incidence of disomy for chromosomes 8, 9, 13, 16, and 21 in 96,292 sperm and found them all to be roughly the same, 0.26–0.32%. This suggests that nondisjunction for each of these chromosomes is equally likely in male meiosis and that the extra chromosome does not affect spermatogenesis. They extended this to chromosome 1 the following year, with a similar result: approximately 0.2% disomy for chromosomes 1 and 16. Since approximately 1 in 500 sperm is disomic for chromosome 1, what accounts for the extreme rarity of trisomy 1, even in early abortuses? Lethality before implantation or soon after seems the most likely explanation. This explanation is supported by the finding of trisomy 1 in an eight-cell preimplantation embryo (Watt et al., 1987).

Incidence of Nondisjunction in Spontaneous Abortions, Stillborns, and Liveborns

There is no direct evidence that any type of chromosome imbalance interferes with the formation of a gamete that is able to participate in fertilization, but analysis of embryos indicates markedly skewed representations of the various

abnormal karyotypes. Large numbers of embryos from presumably normal pregnancies that were terminated for nongenetic reasons have shown a low frequency of chromosome abnormalities, only a bit higher than that found in newborns. In contrast, a very high frequency of karyotypic abnormalities is seen in embryos that spontaneously abort (Boue et al., 1985). A comparison of the incidence of the various karyotypes in embryos that spontaneously abort at various stages of pregnancy with that in stillborn and liveborn infants provides a measure of the relative lethality of each karyotypic abnormality.

The wealth of information on the incidence of numerical and structural chromosome abnormalities in spontaneous abortuses, stillbirths, and live births is illustrated in Table 11.2. Almost half (47.9%) of all spontaneous abortuses are chromosomally abnormal, with 9.8% polyploid (mostly triploid), 8.6% 45,X, and 26.8% trisomic for one or another chromosome (virtually all trisomies have been seen in abortuses). Nearly 6% of stillbirths are chromosomally abnormal, with 0.6% polyploid, 0.25% 45,X, and 3.8% trisomic. Among live births, about 0.3% are aneuploid: most of these are trisomic, with less than one in a thousand 45,X or polyploid. Jacobs and Hassold (1995) also estimated the frequency of chromosome abnormalities in all recognized pregnancies, based on well-established estimates that 15% of pregnancies are spontaneously aborted and 1% end in stillbirths. Almost 1 in 12 pregnancies involves a karyotypic abnormality: polyploidy in 1.5%, 45,X in 1.3%, and trisomy in 4.3%.

The incidence of abnormal karyotypes is higher the earlier in pregnancy the spontaneous abortion occurs. Delhanty et al. (1997) used multicolor FISH to

Table 11.2. Frequencies of Numerical Chromosome Abnormalities in Various Populations

	Frequency (%)					
Population	**Trisomy**	**Polyploidy**	**XO**	**XXY**	**XXX**	**XYY**
Spontaneous abortions	26.8	9.8	8.6	0.2	0.1	
Stillbirths	3.8	0.6	0.25	0.4	0.3	
Live births	0.3		0.01	0.05	0.05	0.05
All recognized pregnancies*	4.3	1.5	1.3	0.08	0.06	0.04
Survival probability	5.8	0	0.3	55	70	100

*Assumes 15% spontaneous abortions and 1% stillbirths

Source: Adapted from Jacobs and Hassold (1995), with permission, Academic Press

analyze preimplantation embryos that were left over from in vitro fertilization cases. They noted that the chance of a successful pregnancy for an embryo transferred into the uterus after in vitro fertilization (IVF) was 25% (the reason for transferring multiple embryos). This is the same as the chance of conception in any one menstrual cycle in fertile women. Delhanty et al. (1997) studied 93 embryos and found that only half were karyotypically normal. Two were fully aneuploid, 30% were mosaics (usually triploid/diploid), and a few showed chaotic divisions. If IVF embryos are representative of the normal population, these findings offer one explanation for the low pregnancy rate in normal women.

First polar bodies have been used for preimplantation diagnosis of aneuploidy, an appropriate approach because of the preponderance of maternal meiotic aberrations (Munné et al., 1995). An interesting approach to the analysis of female meiosis is the use of FISH with chromosome-specific α-satellite centromeric probes to look for abnormal segregation of chromosomes 13, 18, 21, and X in metaphase II oocytes and the associated polar bodies. Using this method, Dailey et al. (1996) found evidence for an additional or missing univalent chromosome in 15 of 168 oocytes (9%) and aneuploidy in 34 (20%). This is surprisingly high, since they were scoring only four chromosomes. Further studies are needed, because nondisjunction of these four chromosomes is responsible for almost all the aneuploidy seen in liveborn populations.

Different chromosomes show markedly different frequencies of trisomy. Trisomy 16 is present in more than 1% of conceptuses, accounting for nearly a fourth of all trisomies in recognized pregnancies. It is unclear to what extent this overrepresentation is due to a higher frequency of nondisjunction of number 16 and to what extent it is due to differential timing of embryonic lethality. The lethal effect of trisomy 16 usually occurs within a limited period, from 22 to 31 days of gestation, when chromosome studies are feasible (Boue et al., 1985). Trisomy for many of the autosomes may lead to degeneration of the embryo at a stage before chromosome studies are possible, leading to low estimates of their frequency. Trisomy 1 has never been seen in abortuses, but was observed in an eight-cell preimplantation embryo (Watt et al., 1987). This is unlikely to be the case for trisomies 21, 18, and 13, which are seen even in liveborns. Furthermore, a recent study of metaphase II oocytes found a preponderance of chromosome 16 among prematurely separated chromatids (Angell, 1997), suggesting that this chromosome indeed has a preferentially high rate of nondisjunction.

Causes of Meiotic Nondisjunction

Do mutant genes play any role in meiotic nondisjunction? None has yet been identified, although one mutation leading to mitotic nondisjunction is described later in this chapter. In principle, any genetic or acquired defect in centromeric function could lead to aneuploidy. Bernat et al. (1991) showed that microinjection of antibodies to kinetochore proteins disrupted the assembly of kinetochores and led to aneuploidy and micronucleated cells. Mitotic cells from scleroderma patients who produce antibodies to the kinetochore protein CENP-C have a slight increase in aneuploidy (Jabs et al., 1993). The alkaloid colchicine specifically destroys the spindle if given in sufficient dosage and at lower dosage can lead to nondisjunction. However, such agents have not been implicated as a cause of human trisomy. Preconception exposure to ionizing radiation has been suggested as a minor cause of nondisjunction, but studies in human populations have not supported this claim (Tease, 1988). No increase in nondisjunction has been found in the survivors of the atomic bombing of Hiroshima and Nagasaki (Awa et al., 1987).

The most important (cyto)genetic cause of nondisjunction is the presence of an abnormal karyotype in either parent. Aberrant meiotic segregation in translocation heterozygotes is discussed in Chapter 16. Here we need only note that 2:1 segregation of a chromosome in oocytes or spermatocytes trisomic for that chromosome is a well-established cause of trisomy 21. Nearly half the progeny of 21-trisomic women are themselves 21-trisomic, although 21-trisomic women rarely become pregnant. Much more common is germline (gonadal) mosaicism in the father or mother of a 21-trisomic individual. Penrose pointed out, more than 30 years ago, that as many as 15% of the mothers or fathers of 21-trisomics have minimal phenotypic features of Down syndrome, suggesting the presence of mosaicism in such parents. Mosaicism has indeed been demonstrated in some of these parents, and this may account for the fact that couples with one trisomic child have a 10-fold increase in the risk of having another.

Maternal Age, Recombination, and Mechanisms of Nondisjunction

The most important predisposing factor for nondisjunction is increased maternal age. Paternal age has a very small effect on the incidence of nondisjunction.

The incidence of disomic sperm increases by a factor of about 2.5 from 20–29 years of age to over 50 years of age (Griffin et al., 1995), whereas the incidence of trisomy increases exponentially with rising maternal age after age 30 or so. At a maternal age of 20 years, the incidence of 21-trisomic children is 0.4 per 1000 newborns; for women age 45 years and over, the risk has increased over 42-fold, to 17 per 1000 newborns (Hassold and Jacobs, 1984). A similar maternal age effect is found for 18-trisomy, 13-trisomy, and most of the other autosomal trisomies found in spontaneous abortuses. The 10–15% of pregnancies in women over 35 years of age account for one-third to one-half of aneuploid offspring. A smaller maternal age effect is seen for XXX and XXY. The incidence of 45,X, on the other hand, is virtually independent of maternal age. Studies of the Xg blood group gene, which is located on the X chromosome, show that in 78% of XO cases the gamete without a sex chromosome came from the father (Sanger et al., 1971). Similar results have been obtained with molecular methods (Mathur et al., 1991).

In some families, two or more sibs with aneuploidy of different chromosomes have been seen, such as trisomy 13 and 45,X, trisomy 21 and 49,XXXXY, or trisomy 18 and trisomy 21. One karyotypically normal couple had three offspring, one each with trisomy 21, 18, and 13. They were born at maternal ages of 40 to 43 years (Fitzpatrick and Boyd, 1989). No cause other than advanced maternal age has been established in this or similar families. The same is true for cases of double aneuploidy, such as XXY and 21 trisomy. Reddy (1997) observed only 22 cases of double trisomy and one of triple trisomy among 3024 spontaneous abortuses, a frequency even less than that expected if the two aneuploid events were independent of each other. They also occurred at an older mean maternal age.

The generally exponential increase in the frequency of nondisjunction with increasing maternal age is correlated with a decline in genetic recombination frequency, for example, for chromosomes 21, 18, 16, and 15 (Robinson et al., 1993; Sherman et al., 1994; Hassold et al., 1995). Chromosome 16 has a genetic length of 172 cM in controls but only 120 cM in trisomy 16 pedigrees. More important is the region of reduced recombination: the normally 60-cM central region of chromosome 16 in controls is 0 cM long in trisomy 16 pedigrees! That is, there is *no recombination* (and *no chiasmata*) around the centromere in female meioses leading to 16 trisomics. Similar results are seen for chromosome 21, although this appears to be true only for meiosis I errors (Fig. 11.2).

Chiasmata stabilize bivalents in late prophase I, when homologous centromeres repel each other and homologues appear to be held together only by

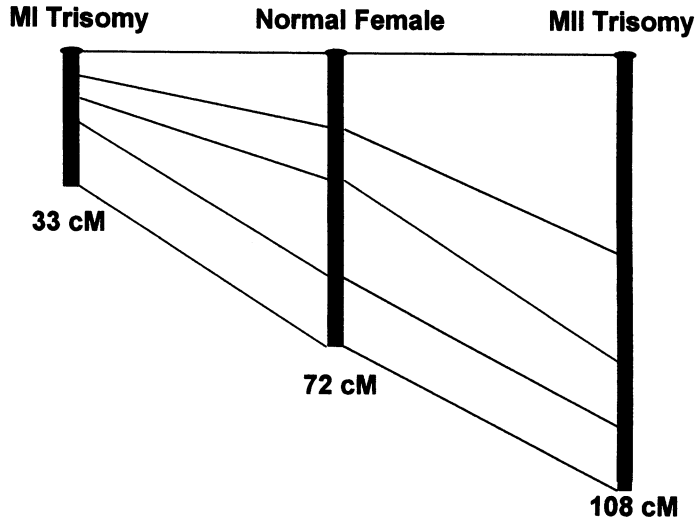

Figure 11.2. Meiotic recombination is reduced in maternal age-related trisomy 21 due to meiosis I errors but increased in that due to meiosis II errors (courtesy of Stephanie Sherman).

their chiasmata. Without a chiasma, the bivalent is likely to fall apart, yielding two univalents. Such univalents have been seen in metaphase II oocytes, as expected in the classical model of nondisjunction (Fig. 11.3; Kamiguchi et al., 1993; Lim et al., 1995). However, Angell (1991; 1997) has marshalled impressive evidence that nondisjunction usually arises in another way (Fig. 11.4). She adapted an improved method for studying the metaphase II oocytes obtained as a by-product of in vitro fertilization. She noted that univalents were much less common than extra or missing chromatids and proposed a novel mechanism of nondisjunction (Angell, 1991). Recently, she presented confirmatory evidence from the analysis of 200 metaphase II oocytes (Angell, 1997). These contained no univalents, but one-third contained prematurely separated chromatids (half-univalents) of three types: 23 + 1/2 (extra chromosome), 22 + 1/2 (missing chromosome), and 22 + 1/2 + 1/2 (balanced, possibly an artifact). Her hypothesis is that the cause of this type of aberration is the premature separation of the bivalent in meiosis I, leading to premature equational division (separation of the chromatids) in MI (Fig. 11.4). Very few MI oocytes have been analyzed, but these have shown some prematurely separated bivalents, particularly in older women.

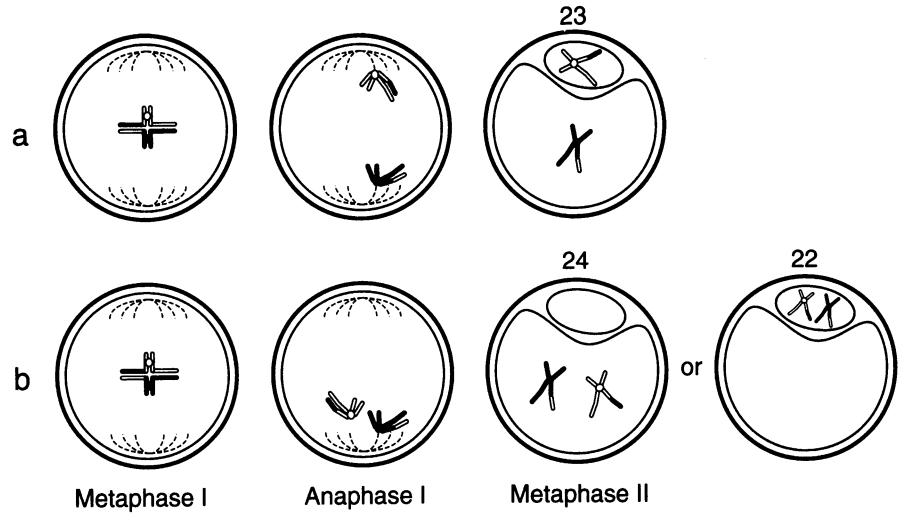

Figure 11.3. Behavior of chromosomes at MI division in oocytes, according to the classic model: (a) Normal disjunction. (b) Nondisjunction (reproduced from Angell, the Am J Hum Genet 61:23, Fig. 1, copyright 1997, the American Society of Human Genetics, with permission of the University of Chicago Press).

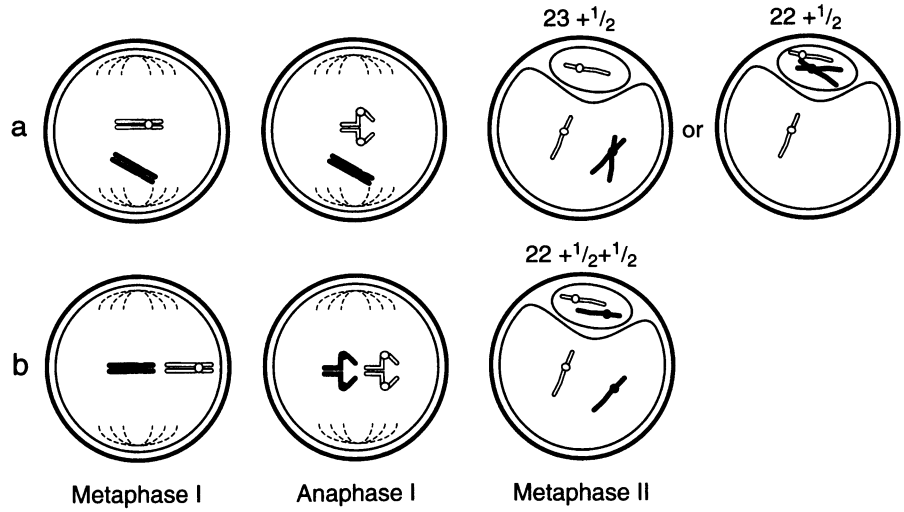

Figure 11.4. (a) Precocious MI division of one univalent leads to 23 + 1/2 and 22 + 1/2 MII oocytes. (b) Precocious MI division of both univalents leads to 22 + 1/2 + 1/2 MII oocytes (reproduced from Angell, the Am J Hum Genet 61:23, Fig. 7, copyright 1997, the American Society of Human Genetics, with permission of the University of Chicago Press).

Parental Origin of Aneuploid Gametes

The marked maternal age effect and minimal paternal age effect on the incidence of aneuploidy indicates that most aneuploidy in older women originates in a maternal meiotic error. This is, in fact, also true for younger women. The development of a large number of highly polymorphic molecular markers for loci scattered throughout the genome (Chapter 29) has provided a means of determining not only the parent of origin of the extra chromosome but whether it arose from an error in meiosis I or meiosis II. Genetic markers close to the centromere are the most useful because they provide the most reliable information on the segregation of the various centromeres; markers farther away are more likely to have been separated from the centromere by recombination.

In individuals with extra sex chromosomes, the extra chromosome was maternal in origin in 90% (45 of 50) XXX females and in 54% (76 of 142) XXY males. In those of maternal origin, the error arose in MI in over two-thirds of cases but in MII in nearly one-fourth and in a postzygotic mitosis in about one-tenth (Table 11.3). The maternal MI errors were associated with the absence of chiasmata in 30%, abnormally distributed chiasmata in 24%, and normal chiasmata in 45%. In all cases with four or five X chromosomes, the

Table 11.3. Percentage of Aneuploidy Attributable to Parent and Stage (MI, MII, or Postzygotic) of Origin, and the Role of Chiasmata, as Reflected by Recombination Frequency

			Maternal			
Karyotype	Paternal	Maternal	Meiosis I	Meiosis II	Postzygotic	Recombination
45,X	80	20				
47,XXX	10	90	66	18	16	Decreased
47,XXY	46	54	70	25	5	Decreased
Trisomy 2	44	56				
Trisomy 13, 14, 15, 22	12	88	68	32		Decreased
Trisomy 16	0	100	100	0		Decreased
Trisomy 18	3	97	29	65	6	Decreased
Trisomy 21	10	90	73	25	2	Decreased

Source: Modified from Jacobs and Hassold (1995), with permission, Academic Press, Fisher et al. (1995), and Savage et al. (1998), with permission, Oxford University Press

extra X chromosomes came from the mother, presumably by nondisjunction in meiosis I followed by nondisjunction again in meiosis II (Hassold et al., 1990).

In trisomy 16, the extra chromosome is always maternal in origin and results from an error in meiosis I (Hassold et al., 1995). Why this is so is unclear, since more than 1 in 1000 sperm is 16-disomic (Pellestor et al., 1996). Trisomy 18 is maternal in origin in 97% (61 of 63) individuals, with 29% due to a meiosis I error, 65% to a meiosis II error, and 6% to a postzygotic mitotic error (Table 11.3). The high density of genetic markers for this chromosome enabled Fisher et al. (1995) to demonstrate the absence of recombination in one-third of those due to meiosis I errors and normal recombination in the other two-thirds due to meiosis I errors and in all 35 due to meiosis II errors. The extra chromosome in trisomies 13, 14, 15, and 22 was maternal in 88% and paternal in 12% (Table 11.3). About two-thirds of the former arose from a meiosis I error and one-third from a meiosis II error. For chromosome 21, nearly one-fourth arose from an error in maternal meiosis II, as shown by homozygosity for markers near the centromere for which the mother is heterozygous. However, there is evidence that in some cases scored as having a meiosis II error, the error was really a failure of segregation of homologues at meiosis I. The evidence for this is the marked maternal age effect in the cases scored as having a meiosis II error. This is not expected, because maternal age does not affect the length of meiosis II but does that of meiosis I (which lasts 10–40 years, roughly). Lamb et al. (1996) proposed that the presence of a decreased number of chiasmata in the pericentromeric region tended to produce premature separation of bivalents at meiosis I. Angell (1997) has confirmed the premature separation of bivalents in meiosis I in older women. However, persistent bivalents have not been observed in any of the hundreds of metaphase II oocytes that have been observed (Kamiguchi et al., 1993; Lim et al., 1995; Angell, 1997).

The Origin of Diploid Gametes and Polyploidy

A triploid zygote may arise in various ways. The egg or sperm may be diploid as a result of restitution in either the first or the second meiotic division. The second polar body may reunite with the egg nucleus. Two sperm may fertilize

the same egg (a rare event, because sperm penetration of the zona pellucida usually triggers a barrier to penetration by other sperm). Jacobs et al. (1978) obtained maximum-likelihood estimates that 66.4% of 24 triploid abortuses arose by dispermy, 23.6% by fertilization of a haploid ovum by a diploid sperm (failure of male meiosis I), and 10% from a diploid egg (failure of female meiosis I). How diploid gametes arise is unclear. Incomplete meiosis I might lead to a restitution nucleus' containing the unreduced diploid complement. Alternatively, endoreduplication in a gonial cell would lead to tetraploid meiocytes in which meiosis would produce diploid gametes.

Tetraploidy is rarer than triploidy among both spontaneous abortuses and live-born infants. This is probably due to the production of fewer tetraploid zygotes rather than to their greater lethality, because there are fewer mechanisms (and these rare) for producing tetraploid zygotes than for producing triploid ones. The most probable origin of tetraploidy is chromosome duplication in a somatic cell in an early-cleavage-stage embryo, a postzygotic event. Fertilization of a rare diploid ovum by an equally rare unreduced sperm may be possible. Another rare event, fertilization of one egg by three sperm, has produced a few tetraploids (Surti et al., 1986), but these have developed as hydatidiform moles rather than fetuses, because of genomic imprinting effects (Chapter 21).

Aneuploidy of Somatic (Mitotic) Origin: Mosaicism

Chromosomal mosaicism is the presence of two or more cell lines with different karyotypes that have arisen from a single fertilized egg. Chromosomal mosaics arise from postzygotic events in somatic cells. Sex chromosome mosaics, the most common, include such types as n – 1/n (XO/XX or XO/XY), n – 1/n + 1 (XO/XXX or XO/XXY), and n – 1/n/n + 1 (XO/XX/XXX). The first two types arise at the first cleavage division, while the third type must arise later, since a normal cell line is also present. Trisomy 21/disomy 21 mosaicism is fairly common, while mosaicism involving chromosome 18, 13, or 8 is much less common and mosaicism for any other autosome is quite rare. Mosaicism usually arises by loss of a chromosome from one daughter cell, but it can also arise by mitotic nondisjunction, producing n – 1 and n + 1 daughter cells. Examples of this are common for the sex chromosomes but are almost never seen for the autosomes. This probably reflects the lethality of autosomal monosomy, even at the cellular level, since there is abundant evidence that autosomal mitotic nondisjunction does occur.

The use of highly polymorphic genetic markers has shown that a significant proportion of autosomal trisomies originate from postzygotic nondisjunction, including 4.5% of cases of trisomy 21 (Antonarakis et al., 1993). In a study of 63 cases of trisomy 18, Fisher et al. (1995) found a postzygotic origin in both of the cases in which the extra chromosome was of paternal origin and in three of the 61 cases in which the extra chromosome was of maternal origin. Robinson et al. (1998) found mitotic errors to be responsible for nearly 10% (12 of 128) of cases with an extra chromosome 15 of maternal origin.

An unusual genetic cause of mitotic nondisjunction has recently been identified. Two unrelated infants had multiple mosaic trisomies and monosomies (multiple variegated aneuploidy). In repeated leukocyte cultures, premature chromatid separation (PCS) of all mitotic chromosomes was observed in 67–87.5% of the cells. Both parents of each infant showed total PCS in 2.5–47% of their cultured leukocytes but did not have mosaic variegated aneuploidy. The phenotype of the presumptive homozygous infants was one of severe growth retardation, microcephaly, seizures, and multiple malformations (Kajii et al., 1998).

Minimal mosaicism is seen in some older people. The frequency of cells with a 45,X karyotype tends to increase with age in normal XX women, and so does that of XX cells in which the centromere of one X is inactivated (Fig. 22.2). The absence of a functional centromere leads to random segregation of this X chromosome, with some cells lacking it and other cells accumulating various numbers of copies.

References

Angell RR (1991) Predivision in human oocytes at meiosis I: a mechanism for trisomy formation in man. Hum Genet 86:383–387

Angell RR (1995) Meiosis I in human oocytes. Cytogenet Cell Genet 69:266–272

Angell RR (1997) First-meiotic-division nondisjunction in human oocytes. Am J Hum Genet 61:23–32

Antonarakis SE, Avramopolous D, Blouin J-L, et al. (1993) Mitotic errors in somatic cells cause trisomy 21 in 4.5% of cases and are not associated with advanced maternal age. Nat Genet 3:146–150

Awa AA, Honda T, Neriishi S, et al. (1987) Cytogenetic study of the offspring of atomic bomb survivors, Hiroshima and Nagasaki. In: Obe G, Basler A (eds) Cytogenetics. Springer, Berlin/Heidelberg, pp 166–183

Bernat RL, Delannoy MR, Rothfield NF, et al. (1991) Disruption of centromere assembly during interphase inhibits kinetochore morphogenesis and function in mitosis. Cell 66:1229–1236

Boue A, Boue J, Gropp A (1985) Cytogenetics of pregnancy wastage. In: Harris H, Hirschhorn K (eds) Advances in human genetics, Vol 14. Plenum, New York, pp 1–57

Dailey T, Dale B, Cohen J, et al. (1996) Association between nondisjunction and maternal age in meiosis II oocytes. Am J Hum Genet 59:176–184

Delhanty JDA, Harper JC, Ao A, et al. (1997) Multicolor FISH detects frequent chromosomal mosaicism and chaotic division in normal preimplantation embryos from fertile patients. Hum Genet 99:755–760

Fisher JM, Harvey JF, Morton NE, et al. (1995) Trisomy 18: studies of the parent and cell division of origin and the effect of aberrant recombination on nondisjunction. Am J Hum Genet 56:669–675

Fitzpatrick DR, Boyd E (1989) Recurrences of trisomy 18 and trisomy 13 after trisomy 21. Hum Genet 82:301

Griffin DK, Abruzzo MA, Millie EA, et al. (1995) Non-disjunction in human sperm: evidence for an effect of increasing paternal age. Hum Mol Genet 4:2227–2232

Guttenbach M, Engel W, Schmid M (1997) Analysis of structural and numerical abnormalities in sperm of normal men and carriers of constitutional chromosome aberrations. A review. Hum Genet 100:1–21

Hassold TJ, Pettay D, May K, et al. (1990) Analysis of non-disjunction in sex chromosome tetrasomy and pentasomy. Hum Genet 85:648–650

Hassold TJ, Merrill M, Adkins K, et al. (1995) Recombination and maternal age-dependent nondisjunction: molecular studies of trisomy 16. Am J Hum Genet 57:867–874

Hassold TJ, Jacobs PA (1984) Trisomy in man. Annu Rev Genet 18:69–97

Hassold TJ, Jacobs PA, Kline J, et al. (1980) Effect of maternal age on autosomal trisomies. Ann Hum Genet 44:29–36

Hultén M (1974) Chiasma distribution at diakinesis in the normal human male. Hereditas 76:55–78

Jabs EW, Tuck-Muller CM, Anhalt GJ, et al. (1993) Cytogenetic survey in systemic sclerosis: correlation of aneuploidy with the presence of anticentromeric antibodies. Cytogenet Cell Genet 63:169–175

Jacobs PA, Hassold TJ (1995) The origin of numerical chromosome abnormalities. Adv Genet 33:101–133

Jacobs PA, Angell RR, Buchanan IM, et al. (1978) The origin of human triploids. Ann Hum Genet 42:49–57

Kajii T, Kawai T, Takumi T, et al. (1998) Mosaic variegated aneuploidy with multiple congenital abnormalities: homozygosity for total premature chromatid separation trait. Am J Med Genet 78:245–249

Kamiguchi Y, Rosenbusch B, Sterizk K, et al. (1993) Chromosome analysis of unfertilized human oocytes prepared by a gradual fixation-air drying method. Hum Genet 90:533–541

Lamb NE, Freeman SB, Savage-Austin A, et al. (1996) Susceptible chiasma configurations of chromosome 21 predispose to non-disjunction in both maternal meiosis I and meiosis II. Nat Genet 14:400–405

Laurie DA, Hultén MA (1985) Further studies on bivalent chiasma frequency in human males with normal karyotypes. Ann Hum Genet 49:189–201

Lim AST, Ho ATN, Tsakok MFH (1995) Chromosomes of oocytes failing in-vitro fertilization. Hum Reprod 10:2570–2575

Mathur A, Stekol L, Schatz D, et al. (1991) The parental origin of the single X chromosome in Turner syndrome: lack of correlation with parental age or clinical phenotype. Am J Hum Genet 48:682–686

Munné S, Dailey T, Sultan KM, et al. (1995) The use of first polar bodies for preimplantation diagnosis of aneuploidy. Hum Reprod 10:1015–1021

Olson SB, Magenis RE (1988) Preferred paternal origin of de novo structural chromosome rearrangements. In: Daniel A (ed) The cytogenetics of mammalian autosomal rearrangements. Liss, New York, pp 583–599

Patau K (1963) The origin of chromosomal abnormalities. Pathol Biol 11: 1163–1170

Pellestor F, Girardet A, Coignet L, et al. (1996) Assessment of aneuploidy for chromosomes 8, 9, 13, 16, and 21 in human sperm by using primed in situ labeling techniques. Am J Hum Genet 58:797–802

Reddy KS (1997) Double trisomy and spontaneous abortions. Hum Genet 101:339–345

Robinson WP, Bernasconi F, Mutirangura A, et al. (1993) Nondisjunction of chromosome 15: origin and recombination. Am J Hum Genet 53: 740–751

Robinson WP, Kuchinka BD, Bernasconi F, et al. (1998) Maternal meiosis I non-disjunction of chromosome 15: dependence of the maternal age effect on level of recombination. Hum Mol Genet 7:1011–1019

Rudak E, Jacobs PA, Yanagimachi R (1978) Direct analysis of the chromosome constitution of human spermatozoa. Nature 274:911–913

Sanger R, Tippett P, Gavin J (1971) Xg groups and sex abnormalities in people of northern European ancestry. J Med Genet 8:417–426

Savage AR, Petersen MB, Pettay D, et al. (1998) Elucidating the mechanisms of paternal non-disjunction of chromosome 21 in humans. Hum Mol Genet 7:1221–1227

Sherman SL, Petersen MB, Freeman SB (1994) Nondisjunction of chromosome 21 in maternal meiosis I: evidence for a maternal age-dependent mechanism involving reduced recombination. Hum Mol Genet 3:1529–1535

Surti U, Szulman AK, Wagner K, et al. (1986) Tetraploid partial hydatidiform moles: two cases with a triple paternal contribution and a 92,XXXY karyotype. Hum Genet 72:15–21

Tease C (1988) Radiation-induced aneuploidy in germ cells of female mammals. In: Vig BK, Sandberg AA (eds) Aneuploidy, Part B: Induction and test systems. Liss, New York, pp 141–157

Watt JL, Templeton AA, Messinis SI, et al. (1987) Trisomy 1 in an eight cell human preembryo. J Med Genet 24:60–64